Isolation and X-Ray Structures of Reactive Intermediates of Organocatalysis with Diphenylprolinol Ethers and with Imidazolidinones

A Survey and Comparison with Computed Structures and with 1-Acyl-imidazolidinones: The 1,5-Repulsion and the Geminal-Diaryl Effect at Work

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In memoriam A. I. Meyers[3]), who paved the way for the use of heterocycles in stereoselective organic synthesis[4])

Reaction of 2-phenylacetaldehyde with the Me_3Si ether of diphenyl-prolinol, with removal of H_2O, gives a crystalline enamine (**1**). The HBF_4 salts of the $MePh_2Si$ ether of diphenyl-prolinol and of 2-(*tert*-butyl)-3-methyl- and 5-benzyl-2,2,3-trimethyl-1,3-imidazolidin-4-one react with cinnamaldehyde to give crystalline iminium salts **2**, **3**, and **4**. Single crystals of the enamine and of two iminium salts, **2** and **3**, were subjected to X-ray structure analysis (*Figs. 1*, *2*, and *6*), and a 2D-NMR spectrum of the third iminium salt was recorded (*Fig. 7*). The crystal and NMR structures confirm the commonly accepted, general structures of the two types of reactive intermediates in organocatalysis with the five-membered heterocycles, *i.e.*, **D**, **E** (*Scheme 2*). Fine details of the crystal structures are discussed in view of the observed stereoselectivities of the corresponding reactions with electrophiles and nucleophiles. The structures **1** and **2** are compared with those of other diphenyl-prolinol derivatives (from the *Cambridge File CSD*; *Table 1*) and discussed in connection with other reagents and ligands, containing geminal diaryl groups and being used in enantioselective synthesis (*Fig. 4*). The iminium ions **3** and **4** are compared with *N*-acylated imidazolidinones **F** and **G** (*Figs. 9*, *12*, and *13*, and *Table 3*), and common structural aspects such as minimalization of 1,5-repulsion (the '$A^{1,3}$-effect'), are discussed. The crystal structures of the simple diphenyl-prolinol · HBF_4 salt (*Fig. 3*) and of Boc- and benzoyl-(*tert*-butyl)methyl-imidazolidinone (Boc-BMI and Bz-BMI, resp.; *Figs. 10* and *11*) are also reported. Finally, the crystal structures are compared with *previously* published theoretical structures, which were obtained from high-level-of-theory DFT calculations (*Figs. 5* and *8*, and *Table 2*). Delicate details including pyramidalization of trigonal N-atoms, distortions around iminium C=N bonds, shielding of diastereotopic faces, and the π-interaction between a benzene ring and a Me group match so well with, and were actually predicting the experimental results that the question may seem appropriate, whether one will soon start considering to carry out such calculations *before* going to the laboratory for experimental optimizations.

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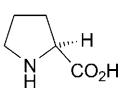
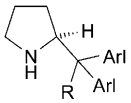
[3]) ...a great chemist, and dear friend and colleague of *D. S.* for over 40 years.

[4]) See his monograph 'Heterocycles in Organic Synthesis', John Wiley & Sons, New York, 1974.

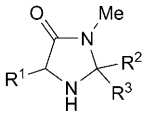
1. Introduction. – The five-membered heterocycles of type **A**, **B**, and **C** may be called the *work-horses* of enantioselective organocatalysis. They are used for enantioselective catalysis of the classical reactions of organic chemistry [1]: aldol addition, aminoalkylation (*Mannich*, *Pictet–Spengler* reactions), arylation, alkylation (intramolecular), amination, oxidation, halogenation, thiolation of α-carbonyl positions, *Michael* additions to α,β-unsaturated carbonyl compounds and nitro-olefins, nitroaldol addition (*Henry* reaction), hydride transfer from dihydropyridine (*Hantzsch* ester), radical coupling of aldehydes with TEMPO and with electron-rich double-bond systems, cyclopropanations, epoxidations, aziridinations, and [3 + 2] and [4 + 2]cycloadditions (*Diels–Alder* reactions)[5][6][7].



A



B



C

The combination of some of these reactions in so-called tandem, multiple-cascade, domino, or multi-component transformations has led to spectacular applications, with stereoselective formation of up to eight stereogenic centers [1l][1v]. Thus, the dream of a synthetic organic chemist has come true: '*The primary center of attention for all synthetic methods will continue to shift toward catalytic and enantioselective variants; indeed, it will not be long before such modifications will be available with every standard reaction for converting achiral educts into chiral products.*'[8][9])

Like all successful types of catalyst, the catalysts of the general structures **A**[6]), **B**, and **C** can, and frequently have to, be optimized for a particular application by combinatorial methods, and they are accessible in both enantiomeric forms, as outlined for the diaryl-prolinols[10]) and imidazolidinones in *Scheme 1*.

The most commonly used diaryl-prolinol derivatives **B** are silylated at the O-atom (R = $OSiR_3$), which allows for additional structural diversification by employing various R groups at Si.

2. Structures of Reactive Intermediates in Organocatalysis by A – C. – The reactive intermediates in the transformations catalyzed by the heterocyclic *sec*-amino compounds **A** – **C** are chiral enamines **D** and iminium salts **E** (*Scheme 2*). For prolin (**A**) catalysis, we have identified and/or isolated and characterized the corresponding non-

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[5]) In this expanding field of organic chemistry, we have to refer to selected reviews and a few seminal original articles [1], and the enumeration of reactions given here cannot be complete.

[6]) Besides proline itself, derivatives such as α-methyl-proline, proline amides, a tetrazole [1r], sulfonylimides, and (aminomethyl)-pyrrolidines [1m] have been used as catalysts.

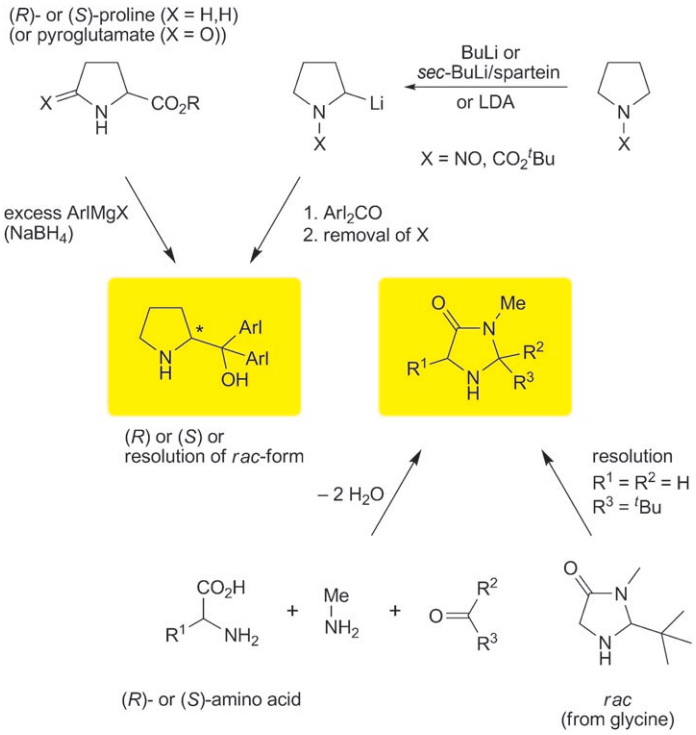
[7]) See also the use of chiral H-bond donors [1j], of Brønsted acids [1t], and of heterocyclic carbenes [1p] as catalysts.

[8]) See summary of a 1990 review article entitled '*Organic Synthesis – Where now?*' [2].

[9]) *Cf.* the title '*In the Golden Age of Organocatalysis*' [1c]; 'Asymmetric Organocatalysis: From Infancy to Adolescence' [1u]; 'Asymmetric Aminocatalysis – Gold Rush in Organic Chemistry' [1x].

[10]) The parent compound **B**, Arl = Ph, R = OH, was originally studied by physiological chemists because of its stimulating activity [3] (effective dose 10 – 20 mg/kg, toxicity LD_{50} = 150 mg/kg [3c]).

Scheme 1. *Combinatorial Preparation of Heterocycles of Type* **B** *and* **C**. The aryl groups of diarylprolinol, from which catalysts **B** (R = OH, $OSiR'_3$, H) are obtained, originate from aryl *Grignard* reagents [3][4] or from benzophenones [5][6]. The imidazolidinones of type **C** are prepared from amino acids, $MeNH_2$, and aldehydes or ketones [7–10]. Thus, an almost indefinite number of substitution patterns of both types of compounds is available for optimizing a catalyst for a particular reaction (a search for *commercial* aryl chlorides, bromides, and iodides, possible precursors of *Grignard* reagents, furnished more than 100,000 examples, and for benzophenones more than 15,000 'hits' were obtained from the *SciFinder Scholar* (version 2007) data base; the number and combinations of commercial amino acids, and aldehydes or ketones is myriad, as well, and, of course, primary amines, other than $MeNH_2$, can be employed (*cf.* the contact of an MeN group with a Me group of ^{t}Bu in *Fig. 10* below).



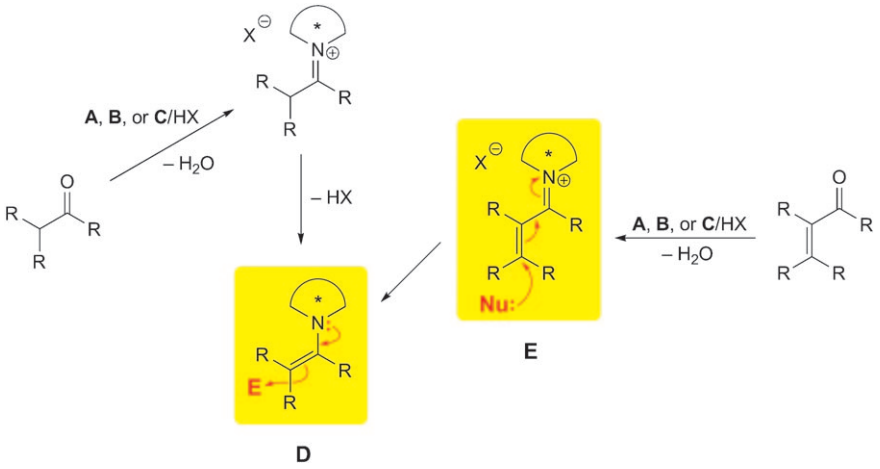
conjugated iminium ion (zwitterion) and the enamine, derived from cyclohexanone [11a]. Structures of enamines and iminium salts of type **D** and **E**, respectively, were not found in the *Cambridge Crystallographic Data File* (CCDF)[11]) as of June 2008. On the other hand, there are many theoretical calculations of the structures of intermediates **D** and **E**, derived from diphenyl-prolinol [12] and imidazolidinone [1q][13][14], using various levels of computation ranging from molecular modeling (MM3)[12]) to density

[11]) For a complete list of X-ray structures of enamines with references to the *CCDF* and to the original literature see [11a]. For new software for searching the *Cambridge Structural Database* (*CSD*) and visualising crystal structures, see [11d].

[12]) In more than a dozen articles published by *MacMillan* and co-workers [1f][1q][13], there are mostly superimposable MM3 models shown to rationalize the observed stereochemical courses of reactions catalyzed by imidazolidinones of type **C**.

functional theory (DFT B3LYP/6-31G(d,p)), and including transition-state structures, with or without solvent. It is tempting to ask why so much effort is being put into computational rather than into experimental work to elucidate mechanistic aspects of organocatalysis. One answer could be that it is so much more rewarding to find new applications of enantioselective catalysis in a short period of time than to use one's energy for cumbersome, excruciating, often slow-moving mechanistic work, *i.e.* the field is in its exploratory discovery phase[13]) before it can become 'contemplating'[14]). Another answer may be that the computer technology and thus the theoretical calculations have become so powerful that experimental results can be reproduced with amazing degrees of accuracy, so that experimental mechanistic investigations may seem to become obsolete; the problem for the simple-minded synthetic practitioner is that a DFT calculation may result in an exact value for an activation energy but will often not provide a qualitative mechanistic model for extrapolations in every-day laboratory work.

Scheme 2. *Reactive Intermediates* **D** *and* **E** *Formed from the Pyrrolidine and Imidazolidinone Catalysts* **A**–**C**, *and Carbonyl Compounds.* The enamine **D** reacts with electrophiles (d^2-reactivity [18]) and the enoyl-iminium ion **E** with nucleophiles (a^3-reactivity). The conjugate, *Michael*-type addition to **E** produces an enamine of type **D**, which, in turn, can couple *intra*- or *inter*molecularly with an electrophilic center. Vinylogous cases, in which a dienamine exerts d^4-reactivity, or a dienoyl-iminium ion a^5-reactivity, are also known [1].



To actually 'see' reactive intermediates of organocatalysis with diaryl-prolinol and imidazolidinone derivatives, we looked for crystalline enamines **D** and iminium salts **E**. While various simple aliphatic aldehydes and enals have so far led only to oily or

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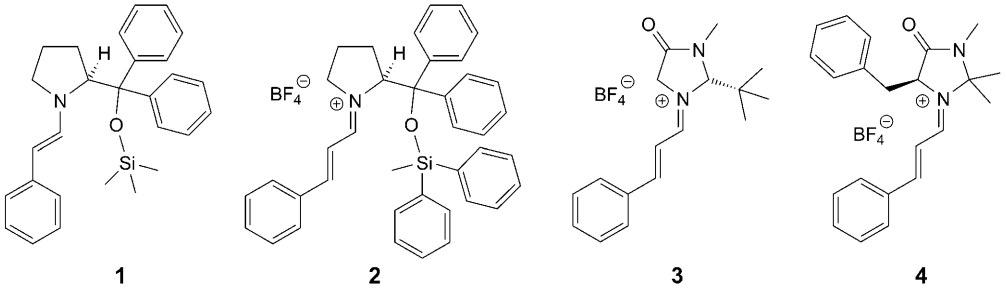
13) In fact, organocatalysis is as old as organic chemistry [15]; for historic-background discussions, see an essay by *Barbas* and co-workers [1b], and Section 11.2 in a book chapter by *MacMillan* and *Lelais* [1f], and [11a]. The ongoing explosive development started in the year 2000 [1a].

14) There are several publications, in which the NMR spectra of *in-situ* generated intermediates are disclosed, mainly as part of supplementary materials; see, *e.g.*, *Blackmond*'s work discussed in Section 4 of [11a] and the following works [1a] (PNAS) [12b][16][17]. See also *Footnote 36*.

otherwise non-crystalline samples, 2-phenylacetaldehyde and cinnamaldehyde gave crystalline derivatives such as the enamine **1** and the tetrafluoroborate salts **2**–**4**.



1 **2** **3** **4**

We used classical methods to prepare these compounds. Thus, the enamine from silyl ether **B** ($R = Me_3SiO$) and 2-phenylacetaldehyde was obtained by condensation with removal of the H_2O formed in a *Dean–Stark* trap. The iminium salts were prepared according to a modified procedure first described by *Leonard* and *Paukstelis*, according to which aldehydes/enals or ketones/enones and BF_4 salts of secondary amines are simply mixed in an appropriate solvent [19]. The enamine **1** and two of the iminium salts, the pyrrolidin and the imidazolidin derivatives, **2** and **3**, respectively, could be recrystallized to give single crystals of sufficient quality for X-ray crystal-structure analysis. The iminium salt **4** derived from the tetrasubstituted imidazolidinone was fully characterized spectroscopically, but could not be crystallized for a single-crystal X-ray structure analysis.

2.1. *Enamine* **1** (*Fig. 1*). As expected, the enamine C=C bond has (*E*)-configuration, and the conformation of the bond between the N-atom and the sp^2-C-atom is s-*trans*, so that the styryl group points away from the C-atom bearing the bulky (silyloxy)(diphenyl)methyl group[15]). The conformation around the exocyclic C,C bond is (+)-*synclinal* (*sc*), with one of the Ph groups on top of the five-membered ring and the O-atom in an *exo*-position. The N-atom is only minimally pyramidalized[16]), and the conjugated π-system, including N, C=C, and Ph, is *almost* perfectly planar (*Fig. 1* and *Entry 1* in *Table 1*).

There is a slight degree of torsion around the exocyclic N–C bond (C–C–N–C(2), 175°; C–C–N–C(5), −11°). Clearly, the *Re* face of the nucleophilic enamine C-atom is like under an umbrella of the $(Me_3SiO)Ph_2C$ substituent, with the diastereotopic *Re* Ph group, and especially one of the Me groups at the Si-atom blocking access of electrophiles from this face, while the *Si* face is open (see the space-filling presentation *c* in *Fig. 1*). This is in agreement with all experimentally determined stereochemical courses of reactions involving silyl ethers of diaryl-prolinol as organo-catalyst [1g][1l][12].

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15) For an *in-situ* NMR spectrum of the dienamine derived from pent-2-enal and *Jørgensen*'s catalyst (with 3,5-$(CF_3)_2$-substituted phenyl rings), see supplementary material in [12b].

16) The N-atoms of *N*-phenylpyrrolidines are planar (*cf.* [20]); compound **1** is a vinylogous *N*-phenylpyrrolidine. For an aliphatic derivative, we argued in a previous work that it would be expected to be pyramidalized on the N-atom (see presentation **J** in [11a], the pyrrolidine ring with an 'obese' substituent in *Table 1*, and discussion in *Sect. 2.3*).

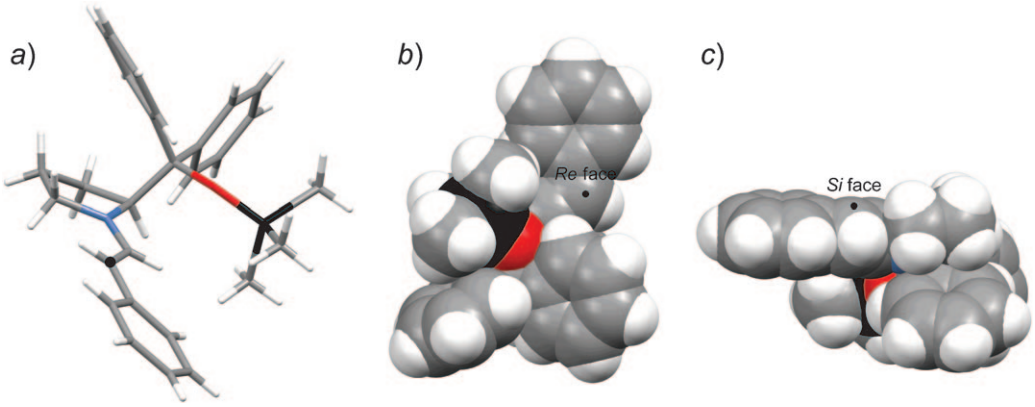


Fig. 1. *Crystal structure of the enamine* **1**. *a*) View of the π-system and the five-membered ring under the 'umbrella' of the (diphenyl)(trimethylsilyloxy)methyl group. *b*) View of the *Re* face of the enamine C(β)-atom. *c*) View along the plane of the π-system with exposed *Si* face. Pyramidality on N-atom, 0.037 Å; torsion angles C–C–N–C(2), 175°; C–C–N–C(5), −11°; O–C–C–N, 61° (*sc-exo*). The black dots indicate the C-atom, at which substituents are attached, as a result of electrophilic attack on the enamine double bond. Since the inducing stereogenic center C(2) of the pyrrolidine ring has (*S*)-configuration the relative topicity (*S*, *Si*) of these reactions can be specified as *like* [21].

2.2. *Iminium Salt* **2** (*Fig. 2*). As in the enamine **1**, the π-system is almost perfectly planar, with hardly any pyramidalization at the N-atom and only a few degrees of torsion around the N=C bond (2–5°) in the two independent molecules of the asymmetric unit (*Fig. 2* and *Entry 2* in *Table 1*). Both, the N=C and the C=C bonds are (*E*)-configured, and the conformation of the connecting single bond is s-*trans* (there would be massive 1,5-repulsion[17]) in the s-*cis* conformation!). Similar to the situation in the enamine **1**, where the Me group at Si plays an important role in sterically hindering access to the nucleophilic C-atom, it is a Ph group at Si of the iminium ion **2**, which contributes substantially to shielding the *Re* face of the electrophilic C(β)-atom (compare *Fig. 1*,*b*, with *Fig. 2*,*c*). To the best of our knowledge, the (methyl)diphenylsilylated diphenyl-prolinol, from which the iminium salt **2** was prepared, has not been used as an organocatalyst. From the structure reported herein, one might expect **B**, R = $MePh_2SiO$, to be an especially selective catalyst.

2.3. *Discussion of Diphenyl-prolinol Derivatives and Comparison with Calculated Structures.* Besides the new structures of silylated diphenyl-prolinol enamine **1**, iminium salt **2**, and of diphenyl-prolinol tetrafluoroborate (*Fig. 3*, and *Entries 1–3* in *Table 1*), we found 19 crystal structures in the Cambridge File (*Entries 4–22* in *Table 1*), 17 of which contain the prolinol moiety itself (free OH group, *Entries 3–19*), while three are methylated at the O-atom (*Entries 20–22*). The large majority of the structures has (O–C–C–N) *gauche* conformation around the exocyclic C,C bond, with the OH group over the five-membered ring (*sc-endo*; see column heading of *Table 1*). This conformation may be the expected one for three reasons: *i*) there is a stereoelectronic

[17]) Here, we use the more general term 1,5-repulsion, rather than $A^{1,3}$-strain, according to the terminology used in the textbook by *Quinkert*, *Egert*, and *Griesinger* [23].

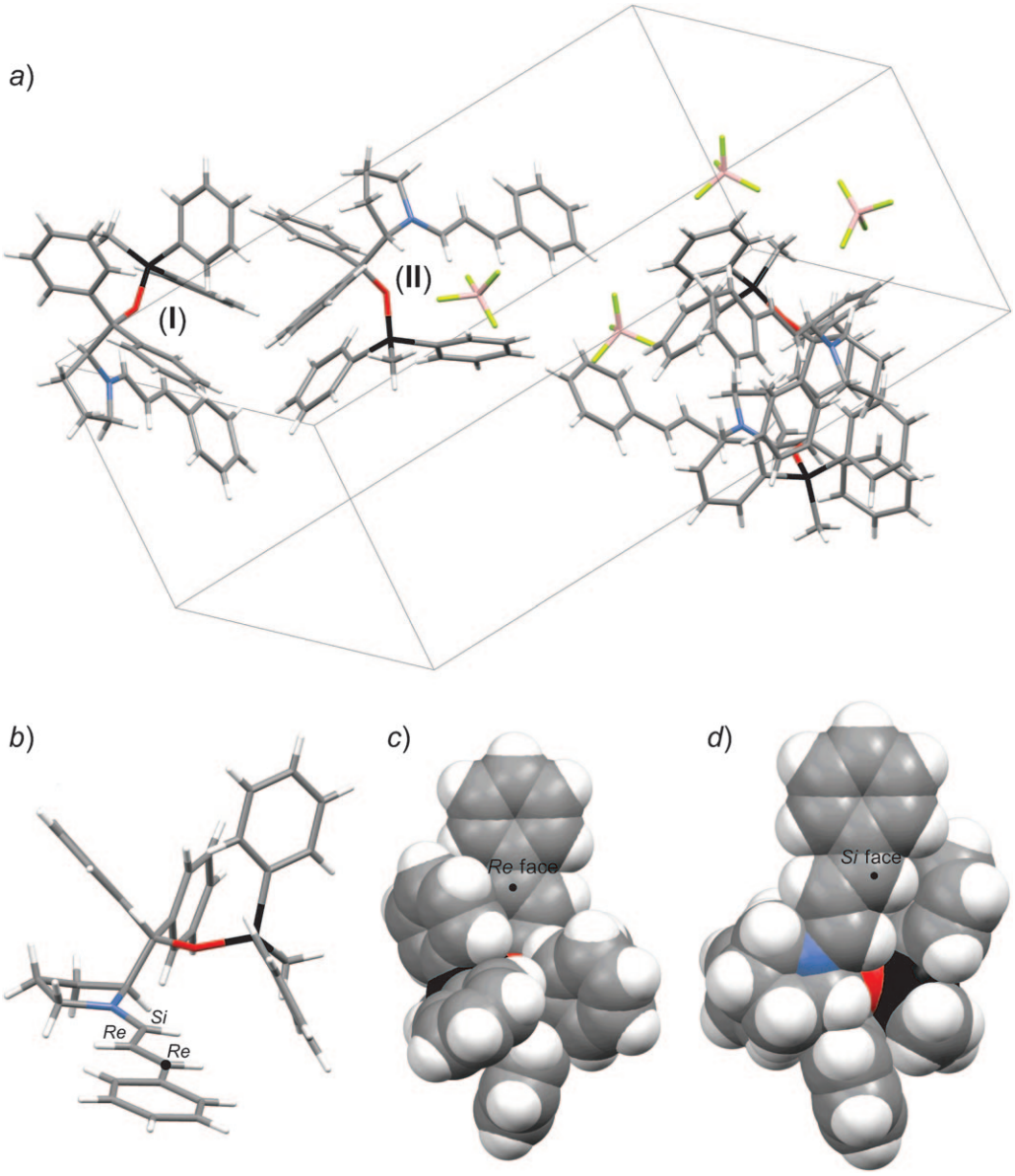
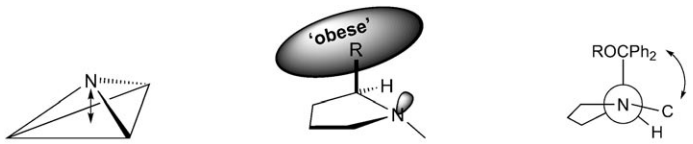
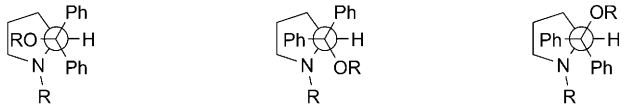


Fig. 2. *Crystal structure of the iminium tetrafluoroborate* **2**. *a*) Two independent molecules **I** and **II** in the unit cell; the two structures are similar. Pyramidality on N-atom, 0.022/0.027 Å, torsion angles, C-C=N–C(2), 178/179°; C–C=N–C(5), –5.5/–5.3°; O–C–C–N, 57.2/56.2° (*sc-exo*). *b*) View of the π-system and the pyrrolidine ring of molecule **I**, with total coverage of the (*Si*,*Re*,*Re*)-face by the (Ph_2MeSiO)Ph_2C group. *c*) and *d*) The *Re* and the *Si* face of the electrophilic C-atom of the enoylimino system in **2** (molecule **I**); access of a nucleophile to the diastereotopic *Re* face is blocked, especially by one of the Ph groups on Si, while the *Si* face is wide open.

Table 1. *Selected Parameters from the X-Ray Crystal Structures of the Silyl Derivatives* **1** *and* **2** (*Entries 1* and *2*, *cf. Figs. 1* and *2*), *and of Diphenyl-prolinols* (*Fig. 3* and *Entries 3–19*) *and Methyl Ethers Thereof* (*Entries 20–22*). The data in *Entries 4–22* have been retrieved from the *Cambridge Crystallographic Data File* (*CCDF*) in May 2008. The pyramidality of the N-atom is given as the distance of N from the plane of its three C-atom bonding partners (in the case of *Entries 21* and *22* two C-atoms and a N-atom; *Δ* [Å], *Dunitz* parameter; the value for a tetrahedral N is *ca.* 0.6 Å, *cf. Entry 19*); all pyramidalizations are such that the substituent on the N-atom is moving away from the large substituent at C(2) of the pyrrolidine. When a trigonal C-atom is attached to the pyrrolidine N-atom (*Entries 5–10*), there may be substantial out-of-plane torsion around this bond (16° in the structure of *Entry 6*), reducing 1,5-repulsion ($A^{1,3}$ effect, *cf. Footnote 17*). The puckering of the pyrrolidine ring varies from structure to structure, there are envelope and twist conformations, with any of the five ring atoms in distinct positions.



pyramidalization on N C–N–C–C



sc-endo *sc-exo* *ap*

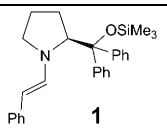
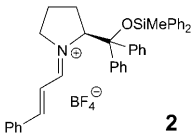
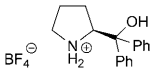
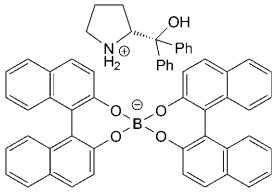
Entry	Molecular formula	*CCDF* Code [ref.]	N-Pyramidality *Δ* [Å]	Torsion angles [°]		
				C–N–C–C	O–C–C–N	
					sc-endo	*sc-exo*
1	 **1**	s020507 [this work]	0.037	– 76.8		61.0
2	 **2**	s260308 [this work]	0.022 0.027	– 76.4 – 79.1		57.2 56.2
3		s030308 [this work]			– 56.2	
4		MIQVEN [3d]			54.6	

Table 1 (cont.)

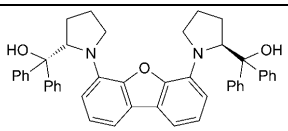
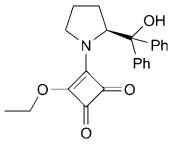
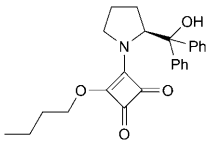
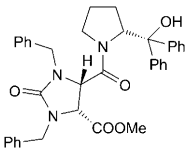
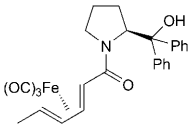
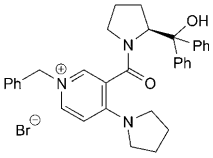
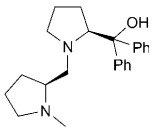
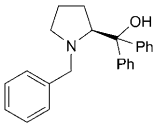
Entry	Molecular formula	*CCDF* Code [ref.]	N-Pyramidality Δ [Å]	Torsion angles [°]		
				C–N–C–C	O–C–C–N	
					sc-endo	*sc-exo*
5		XAWLUD [22a]	0.279 0.385	– 88.4 – 94.4	– 46.6 – 48.7	
6		ICOWUS [22b]	0.03	– 89.2	– 63.6	
7		ACULOZ [22c]	0.095	– 97.0	– 64.3	
8		PILQOR [22d]	0.131	87.9		– 47.9
9		PILXEN [22e]	0.136	– 84.1		46.5
10		CENBED [22f]	0.207	– 97.0	– 64.6	
11		KEVTAH [22g]	0.456	– 110.1	– 54.5	
12		GELROE [22h]	0.426	– 103.1	– 53.3	

Table 1 (cont.)

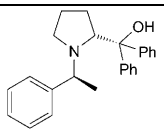
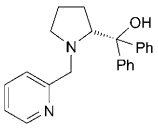
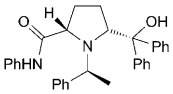
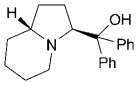
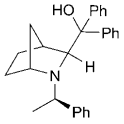
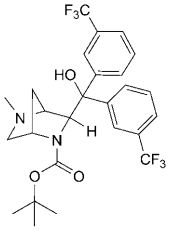
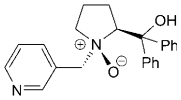
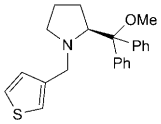
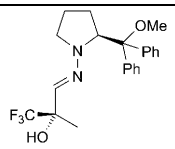
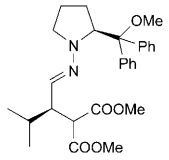
Entry	Molecular formula	*CCDF* Code [ref.]	N-Pyramidality Δ [Å]	Torsion angles [°]		
				C–N–C–C	O–C–C–N	
					sc-endo	*sc-exo*
13		GELTEW [22h]	0.401	100.5	53.8	
14		AQEWEY [22i]	0.462 0.438	105.6 97.2	52.0 48.6	
15		SIHZIT [22j]	0.360	116.1	60.6	
16		UDEMIA [22k]	0.426	– 91.7	– 49.2	
17		ZAQYIZ [22l]	0.445	– 111.8	– 18.8	
18		CEQLIT [22m]	0.256	– 87.2	– 98.5	
19		PESPUY [22n]	0.518	– 88.9	– 59.5	
20		INELES [22o]	0.421	– 105.4	*ap* 178.3	

Table 1 (cont.)

Entry	Molecular formula	*CCDF* Code [ref.]	N-Pyramidality Δ [Å]	Torsion angles [°]		
				C–N–C–C	O–C–C–N	
					sc-endo	*sc-exo*
21		GIWPIL [22p]	0.148	– 82.3	*ap* 177.4	
22		HADMOP [22q]	0.258	– 90.7	*ap* 179.6	

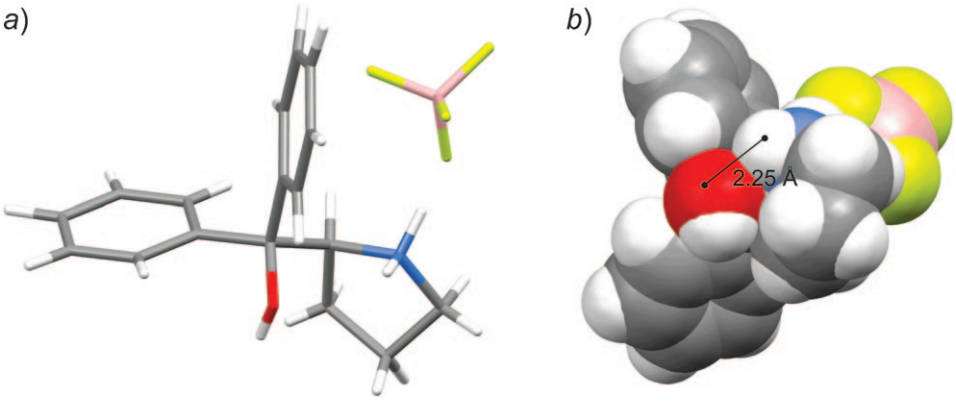


Fig. 3. *X-Ray crystal structure of the HBF_4 salt of (S)-diphenyl-prolinol* **B**, *Arl = Ph, R = OH*. The O–C–C–N bond has *sc-endo* conformation (shown in *a*), with a close distance (2.25 Å) between an NH H-atom and the O-atom of the OH group (shown in *b*; sum of *Van der Waals radii* of H and O, *ca.* 2.6 Å). The exocyclic C,C bond is *quasi*-eclipsed with the neighboring C,H and N,H bonds on a five-ring shape, which comes close to a twist conformation: torsion angles, N–C(2), +14°; C(2)–C(3), +11°; C(3)–C(4), –32°; C(4)–C(5), +40°; C(5)–N, –34°.

preference for the *gauche* conformation of ethane moieties X–C–C–Y (X, Y = R_2N, RO, F)[18]); *ii*) although there is no clear-cut evidence in the crystal structures (*Table 1*, *Entries 3*, *4*, and *11–17*), a geometrically not ideal N···HO or $^{\oplus}$NH···OH H-bond would only be possible in a *sc-endo*-conformation; *iii*) last but not least, the O-atom

[18]) See textbooks on stereochemistry [23][24].

must be considered smaller than a Ph group[19]), which should also favor the *sc-endo*-conformation (O on top of the pyrrolidine ring) over the *sc-exo*- and *ap*-conformations (Ph on top of pyrrolidine ring, see Caption of *Table 1*). Oddly enough, the latter two conformations, *sc-exo* and *ap*, are the ones present in the crystal structures of our two silyl derivatives (*Entries 1* and *2* of *Table 1*) and in the structures of three MeO derivatives (*Entries 20–22*), respectively. Whatever the cause for this conformational change, from *sc-endo* to *sc-exo* to *ap* brought about by putting a silyl or a Me group on the diphenyl-prolinol O-atom, may be[20]), we can see the geminal-diaryl effect for conformational fixation and stereodirection in these structures (*Fig. 4*,*a* and *b*).

This effect is exploited throughout the field of stereoselective organic synthesis: the two Ph or another couple of aryl groups are not only capable of fixing the conformation around a neighboring single bond, the two aryl groups, which, in a chiral molecule, are diastereotopic, also become powerful stereodirectors. This is probably best known with diarylphosphanyl ligands (*cf.* BINAP (=1,1′-binapthalene-2,2′-diylbis(diphenylphosphane), *Fig. 4*,*c*) in transition-metal chemistry [25]. Similarly, the diarylmethanol groups of TADDOLs (=α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols) [26] create two C_2-symmetrically equivalent chiral pockets for stereoselective reactions and host–guest interactions (*Fig. 4*,*d* and *e*). Another recent example is the modified *Evans* auxiliary DIOZ (=4-isopropyl-5,5-diphenyloxazolidin-2-one; *Fig. 4*,*f*), in which the diastereotopic Ph groups improve functional-group ('chemo'-)selectivity and stereoselectivity [27][21]).

Having a list of experimentally determined diarylmethanol structures (*Table 1*), we can make a comparison with calculated structures of this type, with the *caveats* that *a*) crystal packing effects, and/or the position and nature of the counterions in crystalline salts may cause differences in structural details, and *b*) that many theoretical investigations provide gas-phase structures, in which solvent effects are not considered[22]). Structures of diaryl-prolinol derivatives with unprotected OH group [1w][12a] have been calculated[23]), but will not be discussed here, because this type of catalyst is rarely used in organocatalysis.

Of the R_3SiO derivatives, *Jørgensen*'s catalyst (**B**, R = Me_3SiO, Arl = 3,5-$(CF_3)_2C_6H_3$) was the subject of several computational efforts [12]. Most relevant to the X-ray structures of **1** and **2** are the calculated structures of the dienamine[15]) and of

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19) The *A*-value (axial/equatorial on cyclohexane) for OH and OMe is between 0.6 and 1.0, the one for Ph is 2.8 kcal/mol. The *Van-der Waals* radius of the O-atom is 1.4 Å, the 'half-thickness' of a benzene ring is *ca.* 1.7 Å [23][24]. The 'barrel' formed by a rotating Ph group has a radius of *ca.* 3.2 Å.

20) A detailed analysis of the conformations around the C–Ph bonds in these structures might lead to a rationalization.

21) Since the parent compound of the TADDOLs was introduced in 1982, numerous articles on ligands and reagents containing the –[C(Arl)$_2$O]– moiety were published. For a list of examples, as of the year 2000, see Fig. 19 in [26d] and references cited therein. For a most recent review on TADDOL, see [26f]. For more general discussions, see [26c–e][28][29]. A substructure search in *STN International* data base for the [C(Arl)$_2$O] moiety in the period 2000–2008 gives thousands of hits.

22) In many cases, the calculations focus on transition-states structures.

23) The resulting structures all have the *sc-endo*-conformation of the exocyclic C–C bond, as observed in the crystal structures (*Table 1*).

the enoyl-iminium ion shown in *Fig. 5* [12b]. The computation with a high level of theory included an estimation of solvation effects[24]). The similarity of these theoretical structures and the crystal structures is remarkable. In the iminium salt, all characteristic values, *i.e.*, pyramidality and torsion angles, are essentially identical (0.025 *vs.* 0.03 Å, +178° *vs.* +179°, −5.5° *vs.* −6°, +57° *vs.* −59° (*Figs. 1*, *2*, and *5*)). The sign change in the last value (O−C−C−N) is due to the fact that the silylated O-atom is *sc-exo* in the crystal structure and *sc-endo* in the calculated structure. In the enamine, there are larger differences: first and foremost, there is practically no pyramidalization of the N-atom in the crystal structure of the 2-phenylacetaldehyde-derived enamine **1**, while the calculated structure of the pentenal-derived enamine shows an N-pyramidality of 0.21 Å. Thus, theory predicts a structure of the 'obesely' substituted pyrrolidine-enamine, which was discussed as being most likely responsible for the observed selectivities, for steric and stereoelectronic reasons [11a]. Why there is no N-pyramidalization in the crystal structure of the 1-styryl-pyrrolidine **1**, while there is substantial pyramidality in the theoretical structure of an 1-butadienyl-pyrrolidine is difficult to say[25]). The same is true when we ask the question why, in the crystal structures of enamine **1** and iminium salt **2**, the silylated O-atom is in a *sc-exo*-conformation, while the conformation is *sc-endo* in the corresponding calculated structures. The four *meta*-CF_3 groups in *Jørgensen*'s diaryl-prolinol derivatives could be responsible for the structural differences: $(CF_3)_2C_6H_3$ is larger than Ph and may not fit in the position on top of the five-membered ring in an *sc-exo*-conformation (see *Table 1*); furthermore, one of the CF_3 groups in both calculated structures is right on top of the π-system, not only extending the steric shielding of the (*Si*,*Re*,*Si*,*Re*)-face in the dienamine and of the (*Si*,*Re*,*Si*)-face of the iminium ion, as compared to the unsubstituted Ph derivative, but also possibly pushing the π-system down, which could cause pyramidalization on the N-atom of the enamine, but not of the iminium ion (in which planarity with conjugative stabilization is expected to be much more important).

2.4. *Iminium Salts* **3** *and* **4** (*Figs. 6* and *7*). The π-system of the cinnamaldehyde derivative **3** (*Fig. 6*) has (*E*)-configuration around the C=N and the C=C bonds, and s-*trans*-conformation around the C−C bond; (*Z*)-configuration would cause 1,5-repulsion between one of the ^{t}Bu Me groups and the 2′-CH group (*Fig. 6*, *b*)[26]).

The plane of the π-system is slightly bent (*Fig. 6*, *a*); the Ph group is turned out-of-plane by 12°; there is a slight pyramidalization of the iminium N-atom and torsion around the C=N bond (see data in the caption of *Fig. 6*). A comparison of the diastereotopic (*Re*,*Re*)- and (*Si*,*Si*)-faces of the π-system (*Fig. 6*, *c* and *d*) does not disclose a difference in steric hindrance, which would be nearly as pronounced as in the case of the diaryl-prolinole derivatives (*cf. Figs. 1*, *2*, and *5*). A nucleophilic attack from

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[24]) CPCM in Gaussian 03, B3LYP/6-316(d)(CPCM)//B3LYP/6-316(d) [12b].

[25]) Is conjugation, *i.e.*, N-lone-pair delocalization stronger with the styryl or with the pentadienyl group? *N*-Phenyl-pyrrolidine has a planar N-atom (see *Footnote 16*); there is not much known about pyrrolidine-enamine structures (see the discussion in [11a]). The barriers to rotation around the single bond in styrene and in butadiene are similar (*ca.* 3 and 5 kcal/mol, resp.).

[26]) Note that there is 1,5-coplanarity of two Me groups (Me of ^{t}Bu and Me−N) and of a Me and a CH_2 group (Me of ^{t}Bu and CH_2(5)) at distances of 3.2 Å, the *Van-der-Waals* radius of a Me group being 1.8 Å.

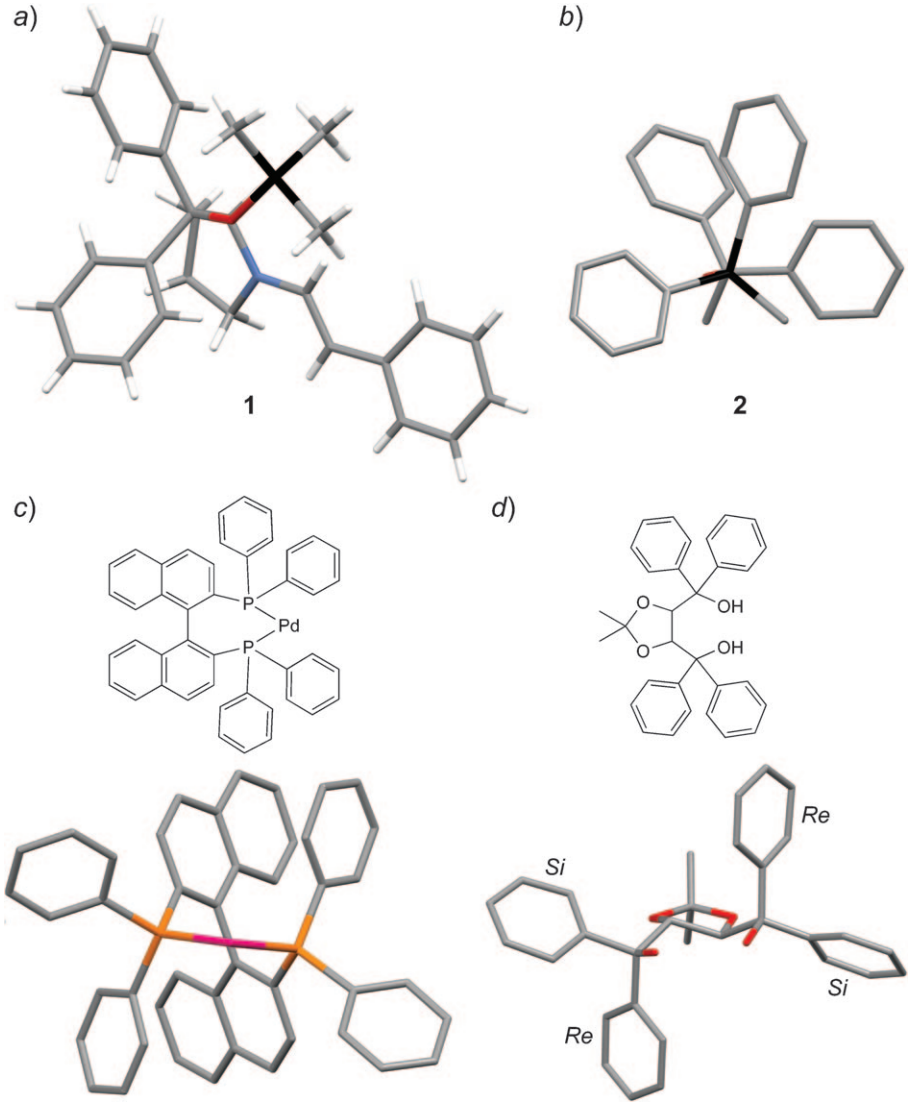

Fig. 4. *The geminal-diaryl effect*. *a*) View at the C-atom bearing the two Ph groups and Me_3Si in enamine **1**. *b*) View along the axis connecting Ph_2C and Ph_2Si (C–O–Si) in iminium ion **2**, with a kind of staggering of the four Ph groups (*cf. e*). *c*) The *quasi*-axial and *quasi*-equatorial Ph groups in a BINAP-Pd complex with room for 'approaches' from the upper left-hand and lower right-hand direction. *d*) The similar C_2-symmetric TADDOL structure with fixed CH–C(OH)-bond conformation and drastically different disposition of the diastereotopic *Re* and *Si* Ph groups. *e*) Transduction of the geminal-diaryl effect on the C-atom to a geminal-diaryl effect on P to give a *quasi*-staggered arrangement of the eight Ph groups; note that Pd is four bonds away from the inducing stereogenic centers on the dioxolane ring; use of this complex for malonate diphenylallylation leads to product of $>99:1$ enantiomer ratio. *f*) Superimposition of DIOZ structures demonstrating a buttressing effect of the equatorial Ph on the CH–$CHMe_2$-bond conformation and a steric-protection effect upon the C=O bond in the oxazolidinone ring by the *quasi*-axial Ph group, which is 'in the way' of the *Bürgi–Dunitz* trajectory[18]). For leading references see accompanying text.

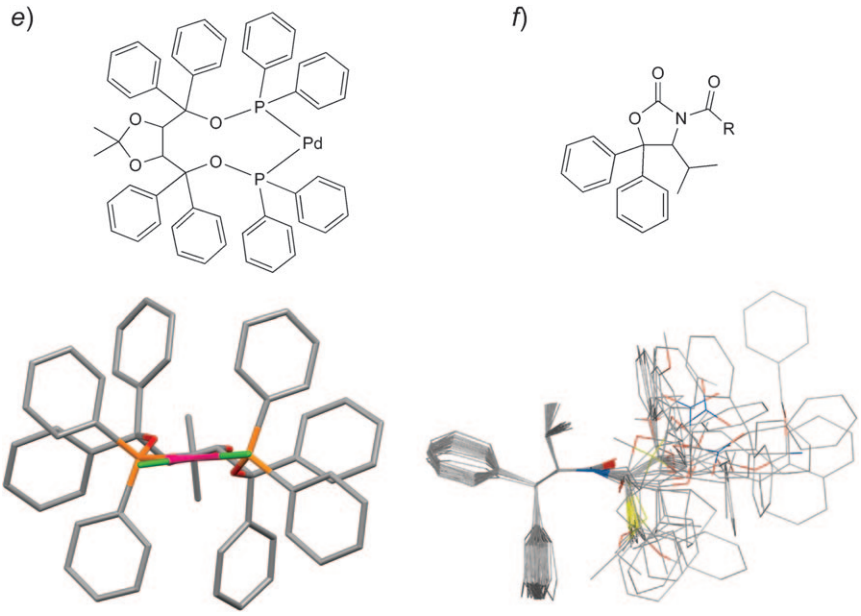

Fig. 4 (cont.)

the *Si* face of the C-atom next to the benzene ring will be hindered by one of the *t*Bu Me groups, especially with bulky reactants (*Fig. 6, d*)[27]).

Of the benzyl-trimethyl-imidazolidinone derivative **4** we have, so far, not been able to obtain single crystals, although samples giving correct elemental analyses were easily prepared. The standard NMR spectrum in (D_6)acetone[28]) of the salt **4** (*Fig. 7*) exhibits one prominent feature: there are two *singlet*s (δ 1.88 and 0.90 ppm) from the geminal Me groups with a shift difference of *ca.* 1 ppm; in the precursor **C** ($R^1 = PhCH_2$, $R^2 = R^3 = Me$), this difference is *ca.* 0.06 ppm (δ 1.85 and 1.79 ppm). To produce more detailed structural information, a 2D-NMR spectrum of the iminium salt **4** in (D_6)acetone was recorded, the interpretation of which allows the following conclusions to be drawn: there must be a certain population of a conformer with the benzylic Ph group facing the *cis*-Me group, which causes the substantial 1-ppm upfield shift of the signal from that Me group; the close distance between Ph and Me is also indicated by a (very weak) nuclear *Overhauser* effect (NOE) between the high-field Me H-atoms and the *ortho*-H-atoms of the Ph group[29]).

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[27]) Analysis of successful applications of the *t*Bu-imidazolidinone (BMI [9]) as catalyst (*cf. Hantzsch* ester) may be compatible [1f][1q][13] with this expectation.

[28]) It is surprising that we noticed iminium-ion interchange between cinnamaldehyde and acetone (present in large excess as a solvent) only to a small extent.

[29]) It is interesting that, according to an *in-situ* NMR spectrum in DMSO by *Gellman* and co-workers [16], in the enamine from **C** ($R^1 = PhCH_2$, $R^2 = R^3 = Me$) and 3-phenylpropanal, the shift difference of the two geminal Me groups is 0.5 ppm (*Fig. 7, c*).

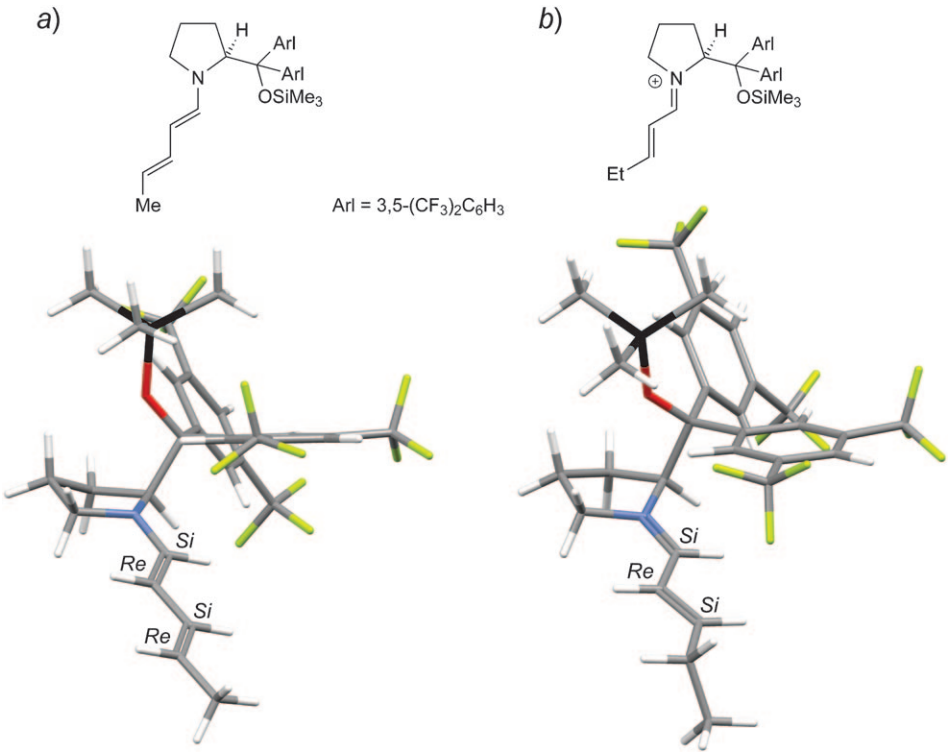


Fig. 5. *DFT-Calculated structures of a dienamine* (*cf. Fig. 1*) *and of an α,β-unsaturated iminium ion* (*cf. Fig. 2*) *derived from the silylated diaryl-prolinol with 3,5-bis-trifluoromethylated Ph groups* [12b]. *a*) Dienamine of pentenal: pyramidality of N-atom, 0.214 Å, torsion angles, C=C−N−C(2), −167°; C=C−N−C(5), −18°; O−C−C−N, −68° (*sc-endo*), s-*trans*-conformation of the exocyclic N−C bond. *b*) Iminium salt of pentenal: pyramidality of N-atom, 0.03 Å, torsion angles, C−C=N−C(2), 179°; C−C=N−C(5), −6°; O−C−C−N, −59° (*sc-endo*), (*E*)-configuration around the N=C bond. Compare with the values in the corresponding X-ray structures in *Figs. 1* and *2*.

2.5. *Comparison of the X-Ray and NMR Structures of the Iminium Ions* **3** *and* **4** *with Analogous Computed Imidazolidinone Structures.* To the best of our knowledge, the most extensive, highest-level DFT calculations of structures and reaction transition states involving imidazolidinones as organocatalysts have been published by *Houk* and co-workers [14]. The iminium ions from the two key imidazolidinones **C**, R^1 = Bn, R^2 = R^3 = Me, and *cis*-**C**, R^1 = Bn, R^2 = ^{t}Bu, R^3 = H, and but-2-enal, and their reactions with pyrroles and indoles were computed in the gas phase and in H_2O. The higher selectivities observed experimentally [31] with the ^{t}Bu derivative were confirmed theoretically. The most stable structures of the two iminium ions obtained in the calculations are shown in *Fig. 8*.

Clearly, and not surprisingly, the *Re* C(2)/*Si* C(3)-face of the electrophilic double bond is subject to more severe steric hindrance than the diastereotopic *Si* C(2)/*Re* C(3)-face. As with the diaryl-prolinoles (*Sect. 2.3*), the similarity between the computed structures (*Fig. 8*), and the NMR and X-ray structures (*Figs. 6* and *7*) is

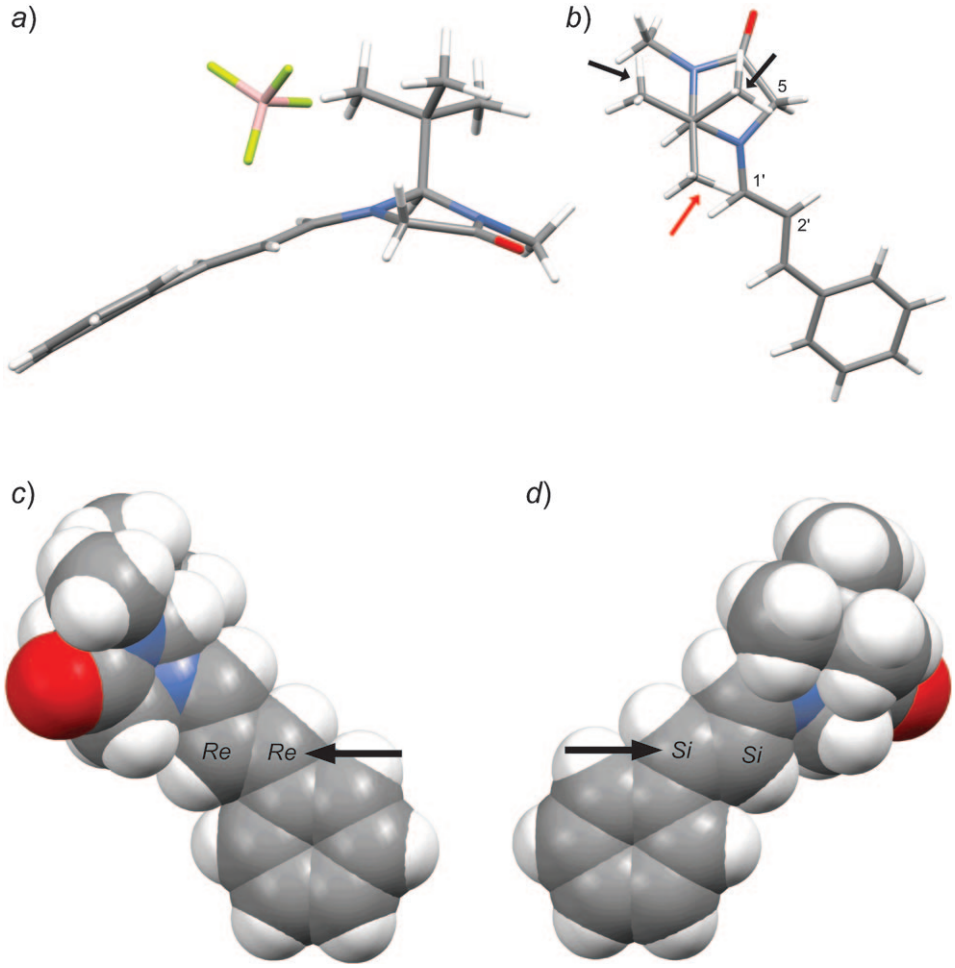


Fig. 6. *Crystal structure of iminium tetrafluoroborate* **3**. The (*S*)-form is shown; for the measurement a racemate crystal was used. *a*) View of the molecule along the plane of the π-system. *b*) View at ion **3** with a *Newman* projection along the ^{t}Bu–C(2) bond; the red arrow indicates the area of severe 1,5-repulsion in the diastereoisomer with (*Z*)-configuration of the exocyclic N=C bond; the black arrows indicate two 1,5-repulsions in this and other 2-(*tert*-butyl)-imidazolidinones (see discussion in *Sect. 2.5*). *c*) and *d*) View of the diastereotopic (*Re*,*Re*)- and (*Si*,*Si*)-face of the C=C bond. Pyramidality of the iminium N-atom, 0.07 Å, torsion angles, C–C=N–C(2), +177°; C–C=N–C(5), +8°.

striking. In the most-stable calculated structure of the benzyl-dimethyl-derivative (*Fig. 8*,a_1), there is an interaction between the benzene ring of the 5-Bn group and the *cis*-2-Me group (distance between the C-atom of the Me group and the center of the aromatic ring 3.8 Å), compatible with the shielding of that Me group in the NMR spectrum of the BF_4 salt **4** (see *Sect. 2.4* and *Fig. 7*). Also, fine details of structural distortions around the iminium N-atom (pyramidality, torsion angles) found in the

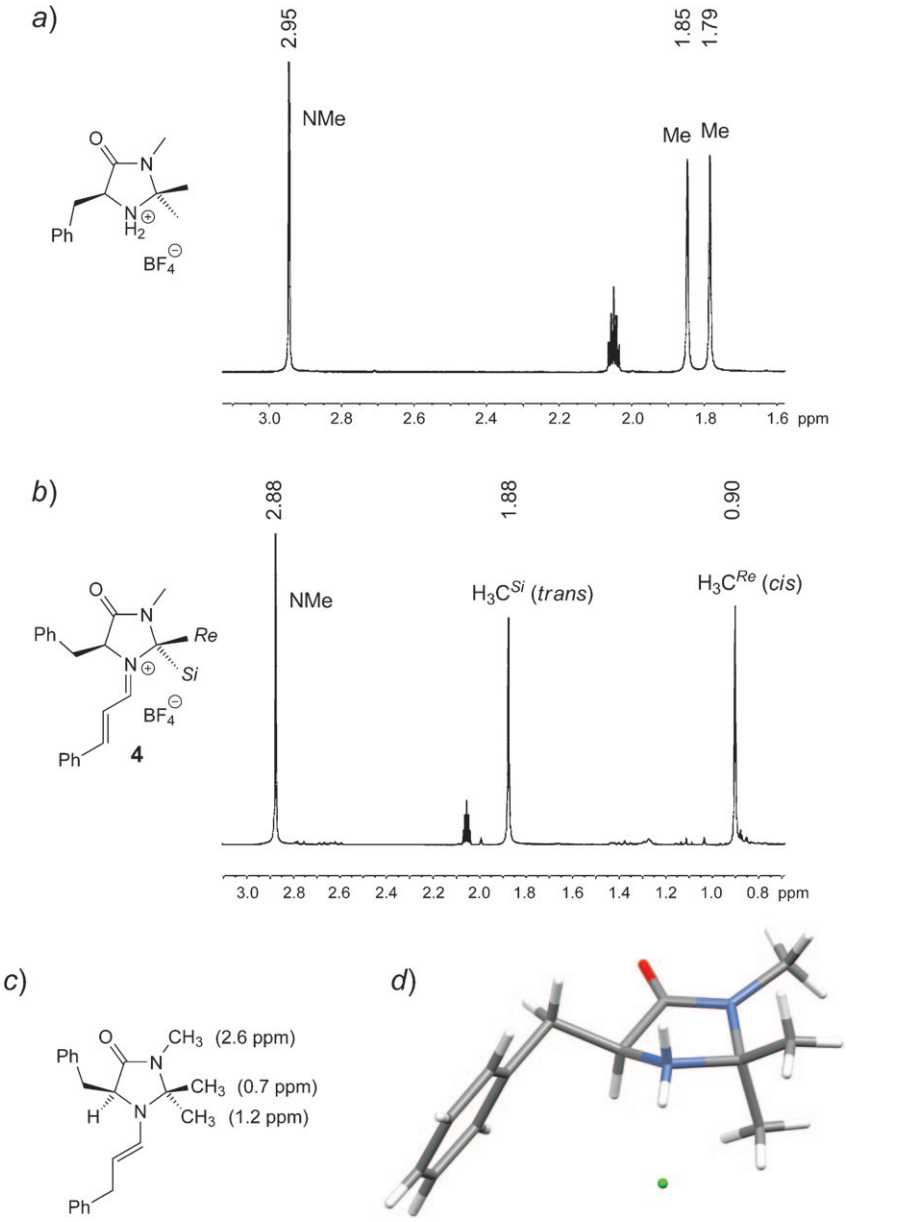


Fig. 7. *Selected NMR data of 5-benzyl-2,2,3-trimethylimidazolidin-4-one derivatives.* Me Region of the ^{1}H-NMR spectra of the imidazolidinone **C** ($R^1 = Bn$, $R^2 = R^3 = Me$) HBF_4 salt (*a*), of the iminium salt **4** (*b*) in acetone, and of the corresponding enamine signals (*c*) in an *in situ* spectrum in DMSO [16], as well as X-ray crystal structure of the HCl salt of the imidazolidinone **C** ($R^1 = Bn$, $R^2 = R^3 = Me$) (*d*) [30]. An *in situ* NMR spectrum of the salt **4**, Cl^- instead of BF_4^-, (in CD_3OD) has been described in the supplementary material of a recent work [17a]. The shielding of the diastereotopic *Re* Me group by the aromatic ring in **4** but not in the precursor is evidence for the population of a conformation as shown in *Fig. 8*,a_1, for the computed crotonaldehyde-derived iminium salt.

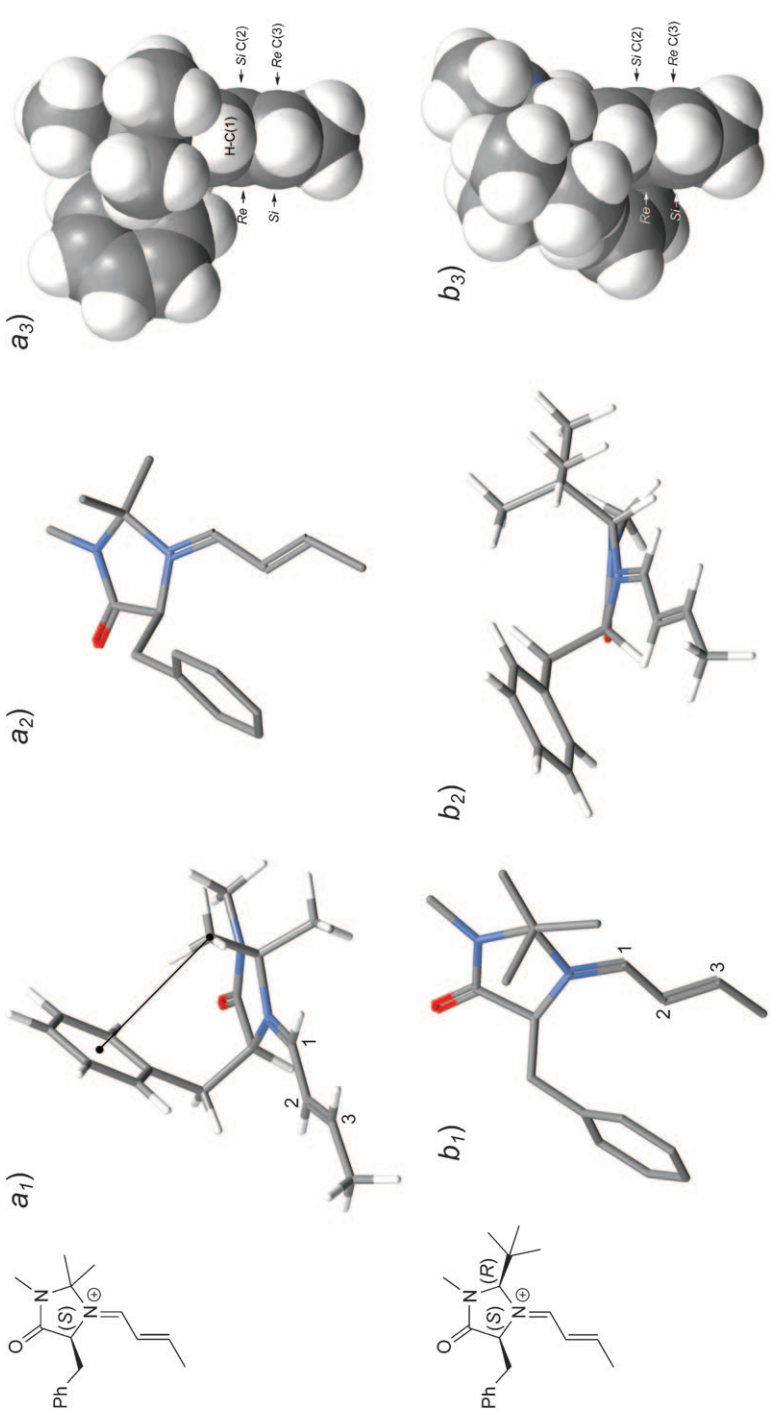
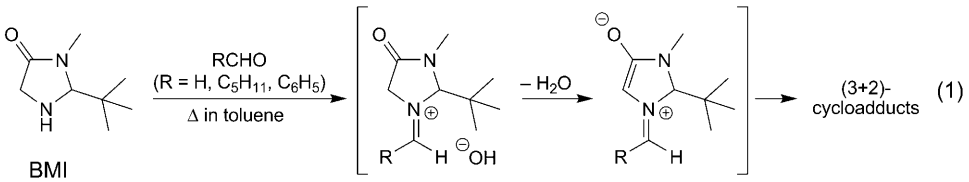


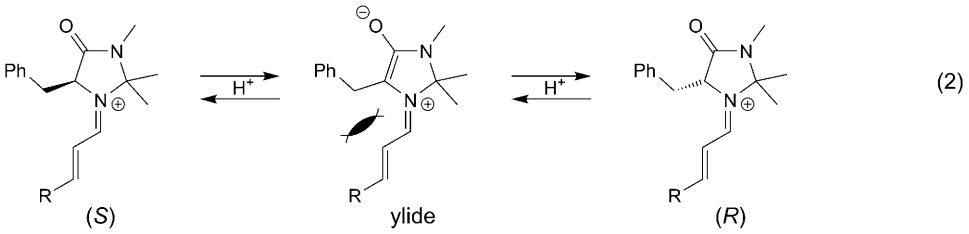
Fig. 8. *Selected structures of iminium ions, derived from (benzyl)(trimethyl)- (*a_1 *–* a_3*) and from* cis*-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidinone (*b_1 *–* b_3*), and crotonaldehyde, as obtained with high-level DFT calculations* [14]. a_1) Most stable structure with a π-HC interaction between the benzene ring and the *cis*-Me group; a_2) second most stable structure (by +0.3 kcal/mol in the gas phase and by +1.7 kcal/mol in H_2O) with the Ph group above the π-system; a_3) view along the π-plane of the conformer shown in a_1, with the less hindered *Si* C(2)/*Re* C(3) face. b_1) Most stable structure with the $PhCH_2$ group over the π-system; b_2) view along the average plane of the five-membered ring with the two large substituents up in *cis*-position and the π-system somewhat bent downwards; b_3) view along the π-plane, with massive shielding of the *Re* C(2)/*Si* C(3) face by the Ph and a Me group. In the conformer a_1, the distance between the *Re* Me C-atom and the center of the benzene ring is 3.8 Å, and the distances between this C-atom and the *ortho*/*ortho'*-C-atoms of the benzene ring are 3.95 and 3.82 Å, respectively (4.8 and 6.0 Å, resp., in conformer a_2); *cf.* the shielding effect observed in the NMR spectrum of **4** (*Fig. 7*). For pyramidalizations and torsion angles in comparison with the values measured in the crystal structure of **3**, see *Table 2*.

crystal structure are predicted by 2004-DFT computations of *Houk* and co-workers [14] (see the comparison in *Table 2*).

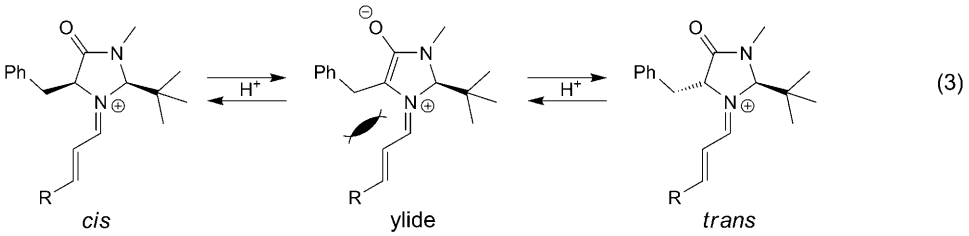
3. Lessons from the Structures of *N*-Acyl-imidazolidinones. – There are some interesting aspects about the configurational stability of the iminium ions derived from imidazolidinones. It is known that such iminium ions can undergo deprotonation in the α-position to C=O with formation of azomethine ylides (*Eqn. 1* [32]). If this would happen in applications of imidazolidinones as organocatalysts, there would be racemization of the benzyl-dimethyl derivative (*Eqn. 2*) and epimerization of the benzyl-(*tert*-butyl) derivative (*Eqn. 3*). This should cause deterioration of enantioselectivity as the reactions proceed. An ylide derived from BMI, on the other hand, could lead to loss of catalyst by reactions with added nucleophiles, for instance, in 1,3-dipolar cycloadditions (*cf. Eqn. 1*). We are not aware of reports about such problems with the imidazolidinone catalysts. There may be good reasons for the phenylalanine-derived ylides not being formed readily: the deprotonation would push the benzylic CH_2 group in-plane with the 2′-CH group causing 1,5-repulsion, as indicated in the ylide *Formulae* in *Eqns. 2* and *3*. Furthermore, the deprotonation/protonation equilibrium shown in *Eqn. 3* is expected to occur with retention of configuration at C(5) for kinetic and thermodynamic reasons: protonation of the ylide from the face *trans* to the ^{t}Bu group should be sterically favored, *and* the *cis*-iminium ion ought to be more stable than the *trans*-isomer. What makes us confident about such statements? It is the lesson we



(1)

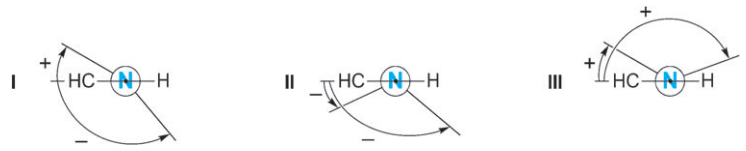


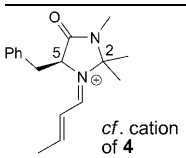
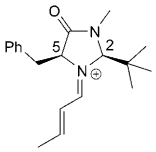
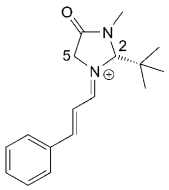
(2)



(3)

Table 2. *Comparison of DFT-Calculated* [14] *with Measured Distortions around N(1) of Imidazolidinone-Derived Iminium Ions.* For definitions, see *Table 1*. For the corresponding structures, see *Figs. 6* and *8*. In all cases, pyramidalizations are such that N(1) moves out of plane of its three bonding partners towards the substituents in 2- and 5-position of the heterocyclic ring (see the 'exaggerated' presentations **I**–**III**). Note that the signs of the torsion angles reverse when we go from *b* to **3**, because the absolute configuration of C(2) is opposite in the two structures. *Cf.* also the presentations *b*, *d*, and *e* in *Fig. 9*.



	Conformation	Pyramidality Δ on N(1) [Å]	Torsion angles [°]	
			C–C–N–C(2)	C–C–N–C(5)
	a_1/a_3 a_2 calculated (*Fig. 8*)	0.023 0.042	–174.2 –174.9	2.3 –1.3
	$b_1/b_2/b_3$ calculated (*Fig. 8*)	0.115	–172.7	–10.0
	measured X-ray structure of **3** (*Fig. 6*)	0.067	177.5	7.9

learned a long time ago from investigations of acyl-imidazolidinones[30]), and, after all, there is a resemblance between an *N*-acyl-imidazolidinone **F** and an imidazolidiniminium ion **G**.

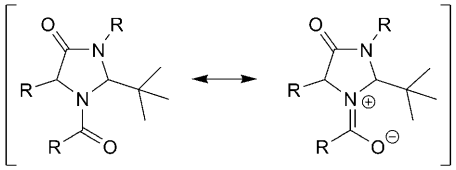
Imidazolidinones of type **C** were first employed in organic synthesis for the preparation of α-branched amino acids [7c], in a process, which was termed 'self-regeneration of stereogenic centers' (SRS; *Eqn. 4*)[31])[32])[33]). With the chiral glycine

[30]) For review articles, see [7c][8]. An electronic version of the article 'EPC Syntheses with C,C-Bond Formation *via* Acetals and Enamines' (Modern Synthetic Methods 1986) [8a] can be obtained from *D. S.* upon request.

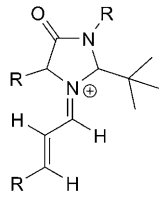
[31]) For recent approaches, see the review article by *Vogt* and *Bräse* [33].

[32]) Originally, we used the term 'self-reproduction' [7a], but our late colleague *V. Prelog* convincingly argued that this term should be reserved for biology.

[33]) For a recent article on this subject, see [34].



F (partial N,C-double bond)



G (full N,C-double bond)

derivative 2-(*tert*-butyl)-3-methylimidazolidin-4-one (BMI) [9] the method was extended (*Eqn. 5*). Early on, it was noticed that the *cis*-2,5-disubstituted imidazolidinones and related heterocycles became thermodynamically more stable than the *trans*-isomers, when the N-atom was *acylated*. Thus, the imines from amino acid *N*-methylamides and pivalaldehyde cyclize to the *trans*-imidazolidinone (unsubstituted in the 1-position) under acid catalysis in the cold, while, upon heating with benzoic anhydride, *cis*-1-benzoylimidazolidinones are the major product (70–90%) [7c] (*Eqn. 6*)[34]). There are numerous reports pointing to the higher stability of *cis*-2,5-disubstituted *N*-acyl-imidazolidine, oxazolidine, and thiazolidine derivatives, as compared to their *trans*-isomers [7b][7c][8][35] (see, *e.g.*, the *trans-cis* isomerizations in *Eqn. 7* and *8* [36]). As discussed previously and as outlined in *Fig. 9* and *Table 3*, the higher stability of *cis*-isomers may be attributed to minimalization of 1,5-repulsions, *i.e.*, to 'the power of the $A^{1,3}$-effect' [8][37]. Pyramidalizations and relevant torsion angles of some *trans*-2,5-disubstituted imidazolidinones are collected in *Table 3* (*Entries 5–11* and *15–17*); as can be seen, things for reduction of 1,5-repulsion look even grimmer in 2,5,5-trisubstituted (*Entries 12–14* and *18*) 2-^{t}Bu-imidazolidinones and in derivatives with a substituent at a trigonal C(5)-atom (*Entries 19–21*).

In the simpler BMI derivatives, carrying a substituent only in the 2-position of the imidazolidinone ring, 1,5-repulsion is still at work: upon *N*-acylation, the ^{t}Bu group, which is *quasi*-equatorial in BMI itself, becomes *quasi*-axial. This causes an increased steric shielding of the face of the ring and of the exocyclic π-system, on which the ^{t}Bu group resides. This is evident from the X-ray crystal structures of Boc-BMI and Bz-BMI, which we have now been able to determine (*Figs. 10* and *11*), and from the comparisons with the prototypical proline case and with the iminium salt **3** in *Fig. 12*.

4. Conclusions and Outlook. – The combinatorial preparation of diaryl-prolinol- and imidazolidinone-derived organocatalysts opens the entry to a wide variety of

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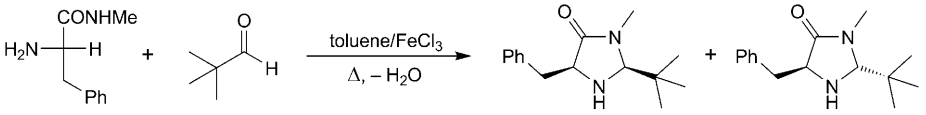
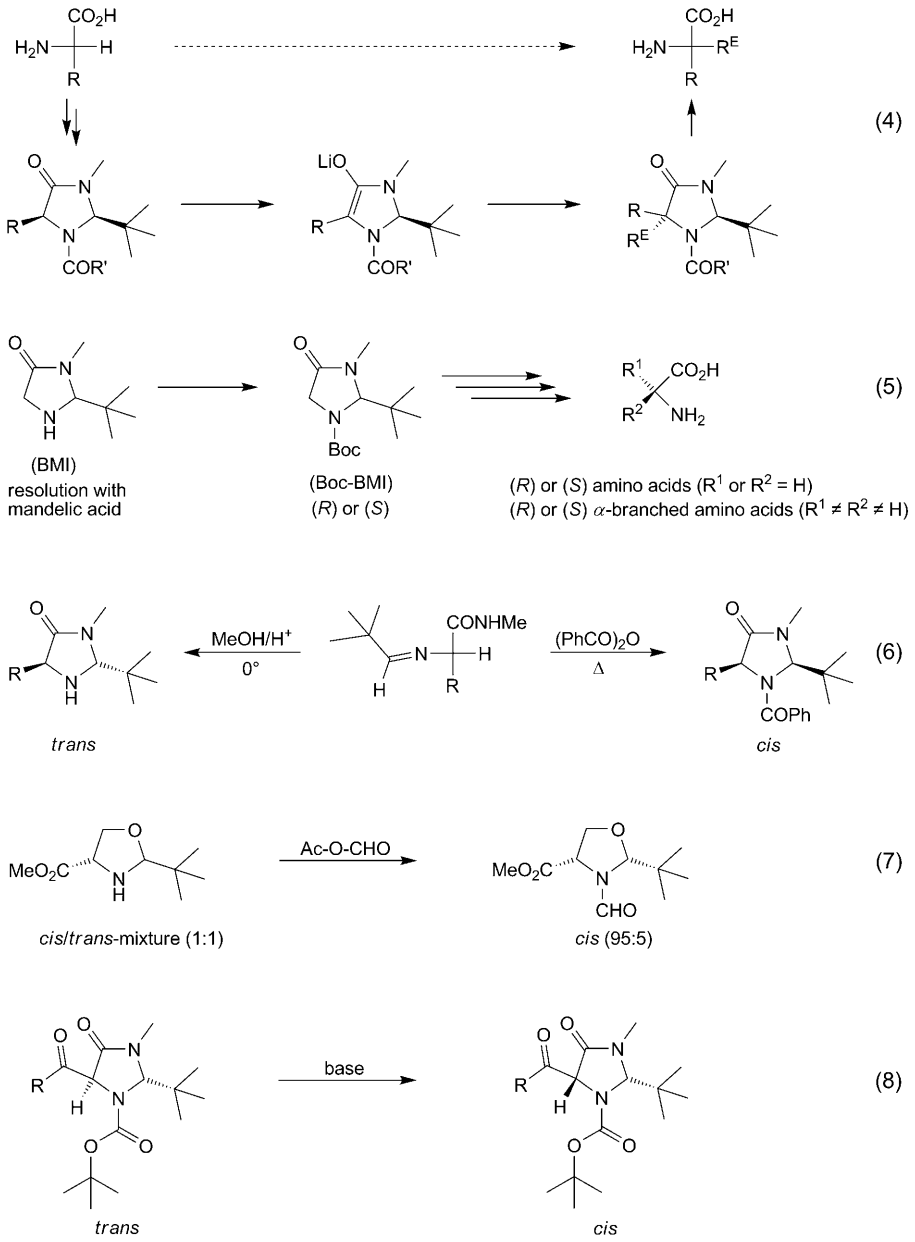
[34]) In the *MacMillan* procedure for preparing the *cis*-benzyl-(*tert*-butyl) derivative, a *ca.* 1:1 *cis*/*trans*-mixture is obtained (under thermodynamic conditions) and separated chromatographically [10c].



ca. 1:1



structurally related systems for substrate-adjusted optimization of the catalysis (*Scheme 1*). As shown previously [11a] and in the present work, the reactive intermediates of this catalysis can be isolated and characterized by conventional preparative and spectroscopic methods. X-Ray crystal structures and NMR spectra of enamines and iminium ions derived from the catalysts may provide structural details

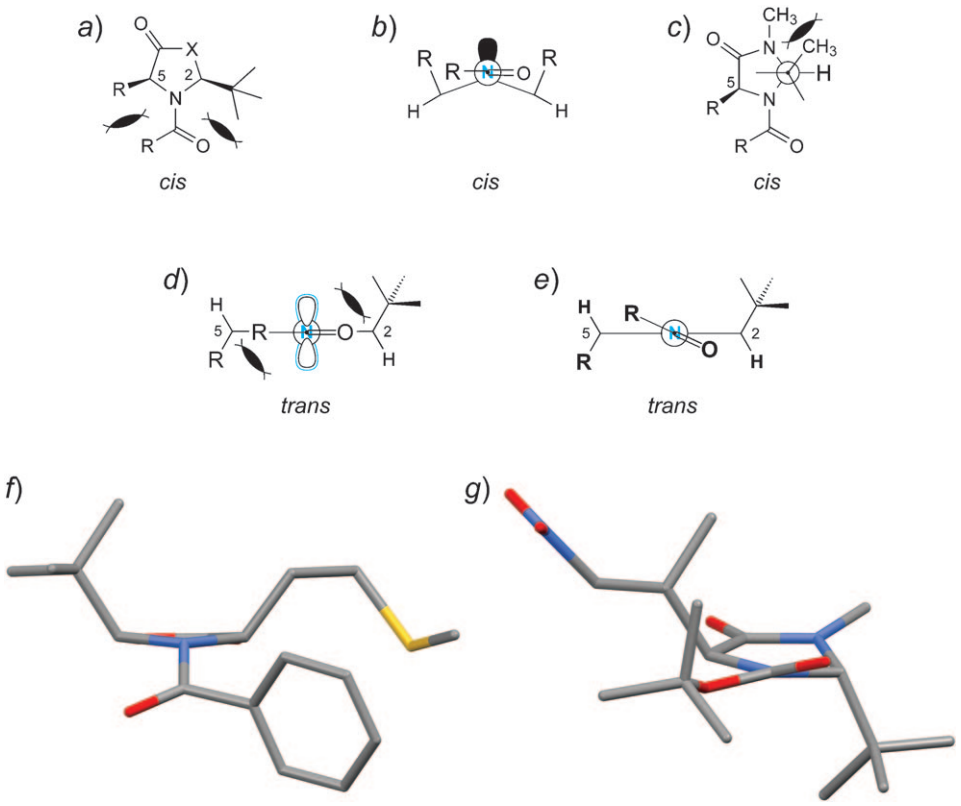


Fig. 9. *Crystal structures of* cis- *and* trans-*2,5-disubstituted imidazolidin- and oxazolidin-4-ones* (*f* and *g*, resp.). Pyramidalization of the acylated N-atom, torsion around the N–CO bond, *quasi*-axial arrangement of the two substituents, and proper folding of the five-membered ring lead to minimalization of 1,5-repulsion (indicated in *a*–*e*). In the *cis*-disubstituted heterocycles, such as the one shown in *f* [35d][38], pyramidalization on N-atom puts the substituents on the carbonyl C-atom closer to the neighboring H-atoms, away from the substituents (*b* and *f*). In almost all structures of this type, the smaller C=O O-atom (short C=O bond, no substituents) is *syn* to the *t*Bu group, and rotation around the amide bond can further relieve conformational strain (see also *Table 3*). In the computed iminium salt (compare *Fig. 8*,*b*, with *f* shown here), this pyramidalization and rotation is less pronounced (energetically more 'costly'). In the less stable *trans*-isomers, such as that shown in *g* [37], the degree of pyramidalization is also smaller; it would increase 1,5-repulsion on one side and decreases it on the other side; rotational deformation, as shown in *e*, on the other hand, can lead to decreased 1,5-repulsion (*cf. Table 3*). The dominant common theme in all structures of this type is minimalization of 1,5-interaction. For a complete collection of X-ray structures of monocyclic 1-acyl-3-alkyl-1,3-imidazolidin-4-ones, we refer to the *CCDF*. Note that in *N*-acyl-piperidines the 1,5-repulsion forces 2- and 6-substituents into the axial position of chair conformations (see the discussion in [37]).

relevant to their reactivities (*Figs. 1*, *2*, *6*, and *7*). In the diaryl-prolinol derivatives, the powerful stereodirecting effect of the geminal diaryl moieties is dominant (*Fig. 4* and *Table 1*). In the imidazolidinone derivatives, minimalization of 1,5-repulsion around the exocyclic N=C bond at the stage of iminium-ion formation is decisive, whereby the steric shielding of one face of the forming π-system is increased (*Fig. 12*).

Table 3. *Pyramidalizations and Torsion Angles in Selected Monocyclic 2-*(tert-*Butyl*)*-3-methyl-1,3-imidazolidin-4-ones and Silyl-enolethers in X-Ray Crystal Structures, Testifying the Distortions around the Exocyclic Amide Bonds.* The values for the new structures are shown in *Entries 1–3* (*cf. Figs. 6*, *10*, and *11*). In the *Formulae*, the conformation around the exocyclic amide bonds are drawn as found in the crystal structures, *i.e.*, mostly s-*cis* with the C=O O-atom on the side of the ^{t}Bu group (exceptions in *Entries 5*, *13*, *14*, and *19*). For better recognition of the kind of distortion, see the *Newman*-type presentations in the caption of *Table 2* and in *Fig. 9*. There is less or hardly any pyramidalization of N(1) in the *trans*-disubstituted structures (*Entries 5–11*; *cf. Fig. 9*, *d* and *e*). The torsion angles around the C(*exo*)–N–C(2)–C(^{t}Bu) is between 80 and 90°, but can be as large as 117° in a 'case of emergency' (*Entry 19*). From the generally small sizes and the signs of the O=C–N–C(2) torsions, it appears that the 'smaller' C=O O-atom causes less 1,5-strain than an OR O-atom or a Ph group.

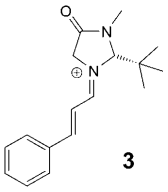
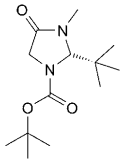
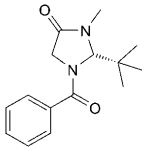
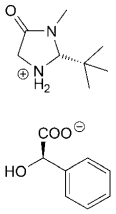
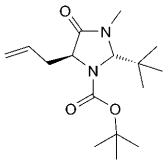
Entry	Molecular formula	*CCDF* Code [ref.]	N-Pyramidality Δ [Å]	Torsion angles [°]		
				C–N–C–C(^{t}Bu)	C–C–N–C(2) O=C–N–C(2) O–CO–N–C(2)	C–C–N–C(5) O=C–N–C(5) O–CO–N–C(5)
1	 **3**	[this work]	0.067	91.5	177.5 – –	7.9 – –
2		[this work]	0.213	105.9	– – 13.2 167.0	– – 161.6 18.6
3		[this work]	0.233	108.1	172.8 – 9.4 –	27.1 – 155.1 –
4		VURBIT [39a]				
5		NAHSEV [39b]	0.097/0.112	90.4/89.5	– – 172.1/ – 170.3 8.4/9.7	– 22.4/26.4 – 157.2/ – 153.6

Table 3 (cont.)

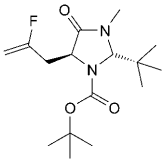
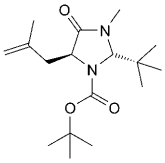
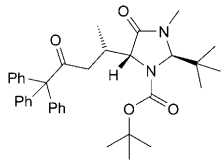
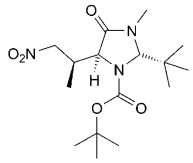
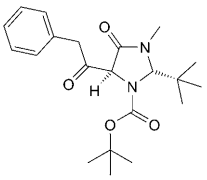
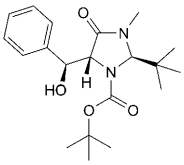
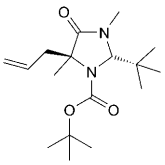
Entry	Molecular formula	*CCDF* Code [ref.]	N-Pyramidality Δ [Å]	Torsion angles [°]		
				C–N–C–C(ᵗBu)	C–C–N–C(2) O=C–N–C(2) O–CO–N–C(2)	C–C–N–C(5) O=C–N–C(5) O–CO–N–C(5)
6		NAHRUK [39b]	0.117	89.1	– 2.6 – 175.9	– – 159.9 21.5
7		NAHSOF [39b]	0.092	84.3	– 6.0 – 172.4	– – 160.2 21.3
8		PATCAO [39c]	0.071	– 84.4	– – 10.8 170.1	– 158.7 – 20.5
9		JOPWUG [37]	0.103	83.5	– 10.6 166.8	– – 154.0 28.6
10		LAXXIR [36c]	0.172	88.6	– 2.0 – 177.4	– – 152.6 28.1
11		JOPXAN [37]	0.007	– 78.7	– – 16.4 163.9	– 162.9 – 17.2
12		NAHSIZ [39b]	0.209	90.6	– – 1.4 – 179.3	– – 151.5 30.7

Table 3 (cont.)

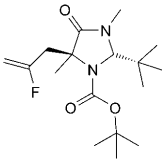
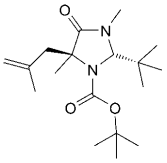
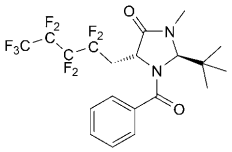
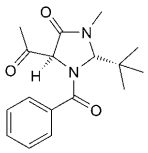
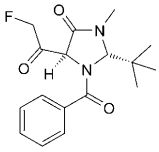
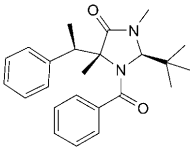
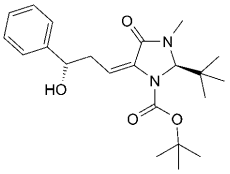
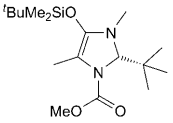
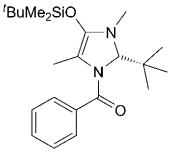
Entry	Molecular formula	*CCDF* Code [ref.]	N-Pyramidality Δ [Å]	Torsion angles [°]		
				C–N–C–C(ᵗBu)	C–C–N–C(2) O=C–N–C(2) O–CO–N–C(2)	C–C–N–C(5) O=C–N–C(5) O–CO–N–C(5)
13		NAHSAR [39b]	0.141	88.6	– – 179.7 0.8	– 20.8 – 158.7
14		NAHSUL [39b]	0.134	84.7	– – 174.6 4.9	– 25.0 – 155.4
15		HEVTIL [39d]	0.101	– 87.3	165.5 – 10.4 –	– 29.7 154.4 –
16		RIQCEZ [39e]	0.206	93.5	– 175.9 – 0.5 –	34.1 – 150.6 –
17		RIQCAV [39e]	0.179	94.6	– 173.2 3.1 –	33.1 – 150.6 –
18		SOSDEJ [39f]	0.237	– 90.8	168.1 – 7.7 –	– 45.8 138.4 –
19		JOPXER [37]	0.281	– 116.9	– – 148.6 32.6	– – 9.5 171.7

Table 3 (cont.)

Entry	Molecular formula	*CCDF* Code [ref.]	N-Pyramidality Δ [Å]	Torsion angles [°]		
				C–N–C–C(*t*Bu)	C–C–N–C(2) O=C–N–C(2) O–CO–N–C(2)	C–C–N–C(5) O=C–N–C(5) O–CO–N–C(5)
20		JIMHOC [39g]	0.287	108.4	– – 17.1 164.9	– – 154.8 27.3
21		JIMHIW [39g]	0.211	102.9	158.5 – 23.1 –	10.7 – 171.0 –

The same effect is operative with *N*-acyl-imidazolidinones, in which the partial double-bond character of the exocyclic amide bond causes 1,5-repulsive interactions; these are minimized by more pronounced distortions (*N*-pyramidalization and out-of-plane rotation around the amide bond) than those seen in a crystal structure of an imidazolidinone-derived iminium salt (*Figs. 6* and *9–12*, and *Table 3*). It is pointed out that the same kind of effect is responsible for the very special role proline plays as structural element in proteins. The structural similarities are demonstrated, once more, by the comparison outlined in *Fig. 13*, wherein three additional types of *N*-acylated heterocycles of synthetic importance are shown, the *Mutter* pseudo-prolines (ψ-Pro) [41], the *Evans*-type auxiliaries [27][42], and the *Garner* aldehyde [43].

The experimentally determined structures and NMR spectra are also compared with structures obtained by high-level-of-theory DFT computations (*Figs. 5* and *8*, and *Table 2*). This comparison reveals striking agreement of delicate structural details between measured and calculated systems[35])[36]). In fact, structural effects predicted by theory were now confirmed by experiment. The same type of DFT investigations, for

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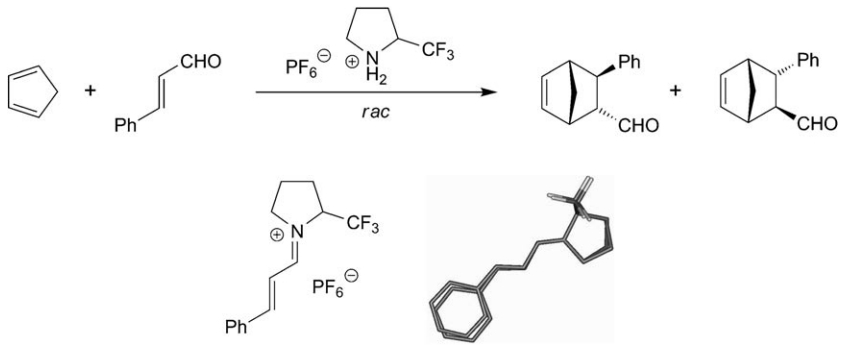
[35]) For recent calculations of the intermediates in proline catalysis, see [11c].

[36]) In a seminal work, *Platts*, *Tomkinson*, and co-workers used *rac*-2-(trifluoromethyl)pyrrolidine · HPF_6 as a *Diels–Alder* catalyst and obtained the same *endo*/*exo*-selectivity as with isolated iminium salt. A superimposition of the X-ray crystal structure and DFT-calculated structure 'shows much similarity' [44].



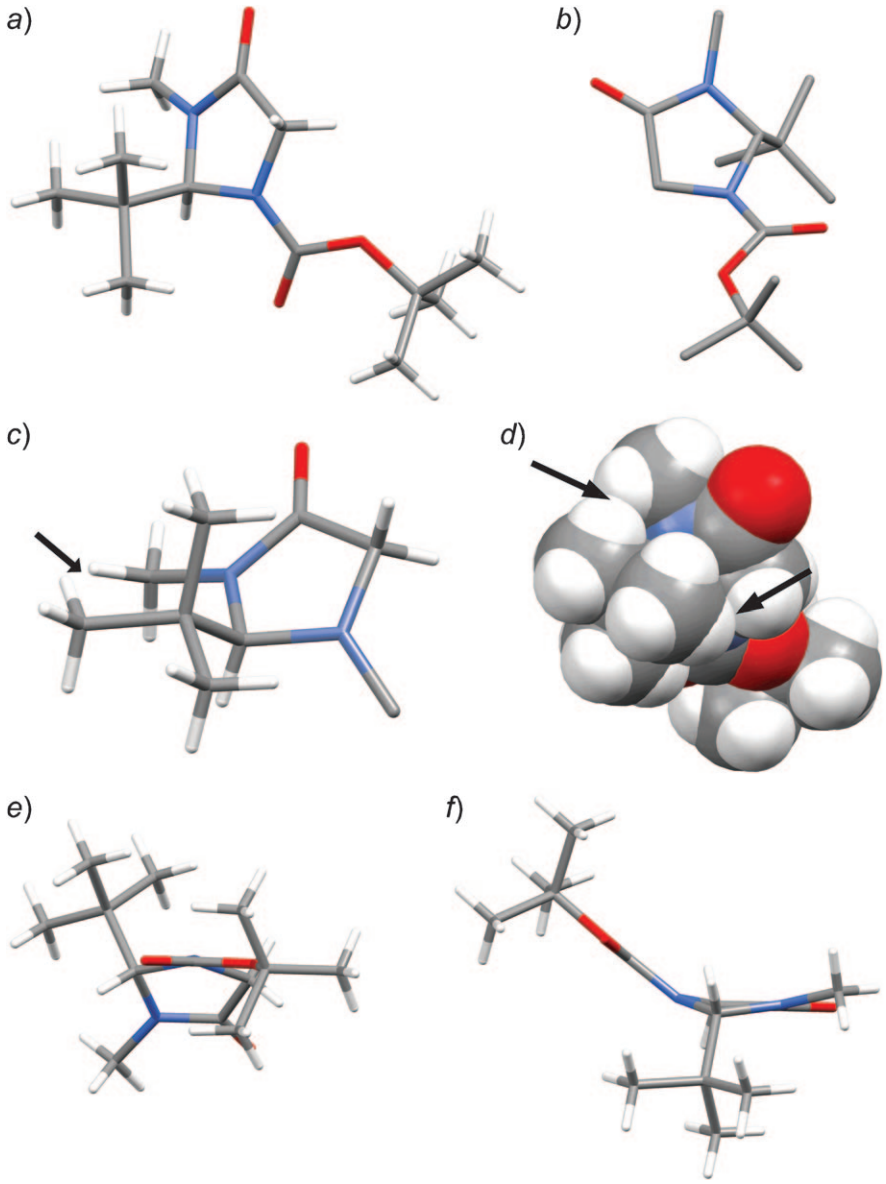


Fig. 10. *X-Ray crystal structure of 1-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-3-methyl-1,3-imidazolidin-4-one* (Boc-BMI). *a*) View at the carbamate and ring plane from the face *cis* to the ^{t}Bu group. *b*) View at the ring plane *trans* to the ^{t}Bu group. *c*) and *d*) 1,5-Repulsive *Van der Waals* contact between ^{t}Bu Me groups, and the N(3)–CH_3 and CH_2(5) group, C,C-distances 3.20 and 3.28 Å, respectively (see arrows). *e*) and *f*) The views along the OC–N axis and along the average ring plane of the heterocycle show the pyramidality of N(1), with reduction of 1,5-repulsion.

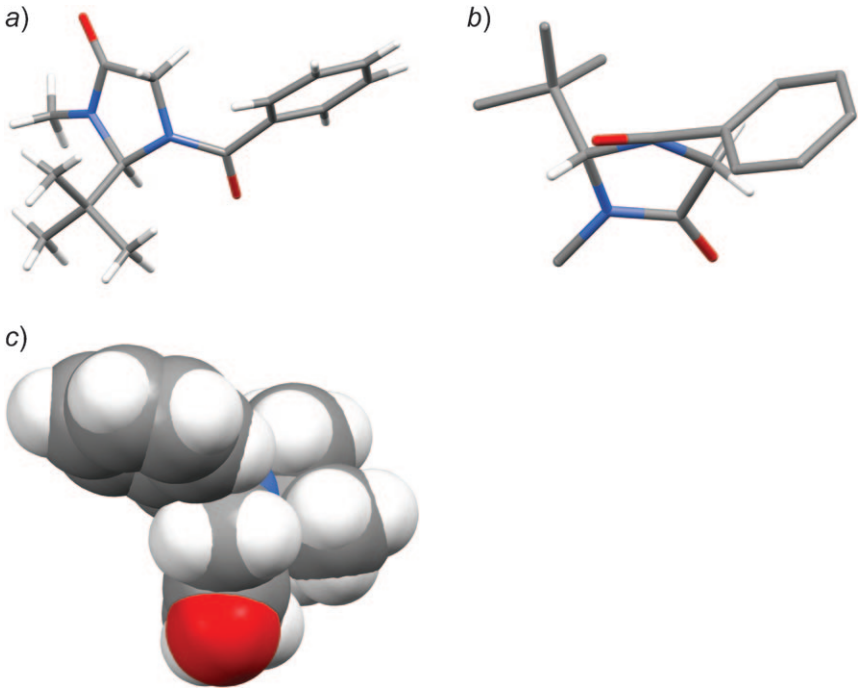


Fig. 11. *X-Ray crystal structure of 1-benzoyl-2-(*tert*-butyl)-3-methyl-1,3-imidazolidin-4-one* (Bz-BMI). *a*) View at the amide and heterocycle plane from the face *cis* to the ^{t}Bu group. *b*) View along the exocyclic amide bond with pyramidal N(1) and a slight torsion around this bond. *c*) One face of the heterocycle is sterically shielded by the Ph group, the other by one of the ^{t}Bu Me groups (*cf.* 'Protecting Groups are not Just Passive Spectators', Scheme 33 in [8b] and [40]).

instance, by *Houk* and co-workers [14], have been also applied to transition-state structures, to reproduce experimentally determined levels of reaction stereoselectivities (relative energies of transition states, even including solvent effects)[37]). With the power of computing increasing exponentially in recent years, one is tempted to raise the question when synthetic organic chemists will start carrying out calculations to choose the best organocatalyst[38]) for a certain reaction before they go to the laboratory, with a good chance of avoiding tedious experimental optimizations.

All experimental details of the work mentioned herein will be published in a forthcoming work, together with results of our ongoing investigations in this field, for

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[37]) For application of a new program (ACE = Asymmetric Catalyst Evaluation), which is faster (requiring less computing power) than DFT calculations, to 44 known 'systems' (*Diels–Alder* and aldol additions), see [45]. The experimental results are reproduced to a reasonably high degree of accuracy. Title of the work: '*Toward a Computational Tool Predicting the Stereochemical Outcome of Asymmetric Reactions*'.

[38]) Organocatalysts, by definition, work in the absence of metal derivatives, *i.e.*, essentially only main-group elements (C, H, N, O, P, S, halogen) are involved in the calculations of 'arrow-pushing' reactions. For these elements, the DFT calculations appear to be especially successful. The situation with reactions catalyzed by transition-metal complexes is far more *complex* [46][47].

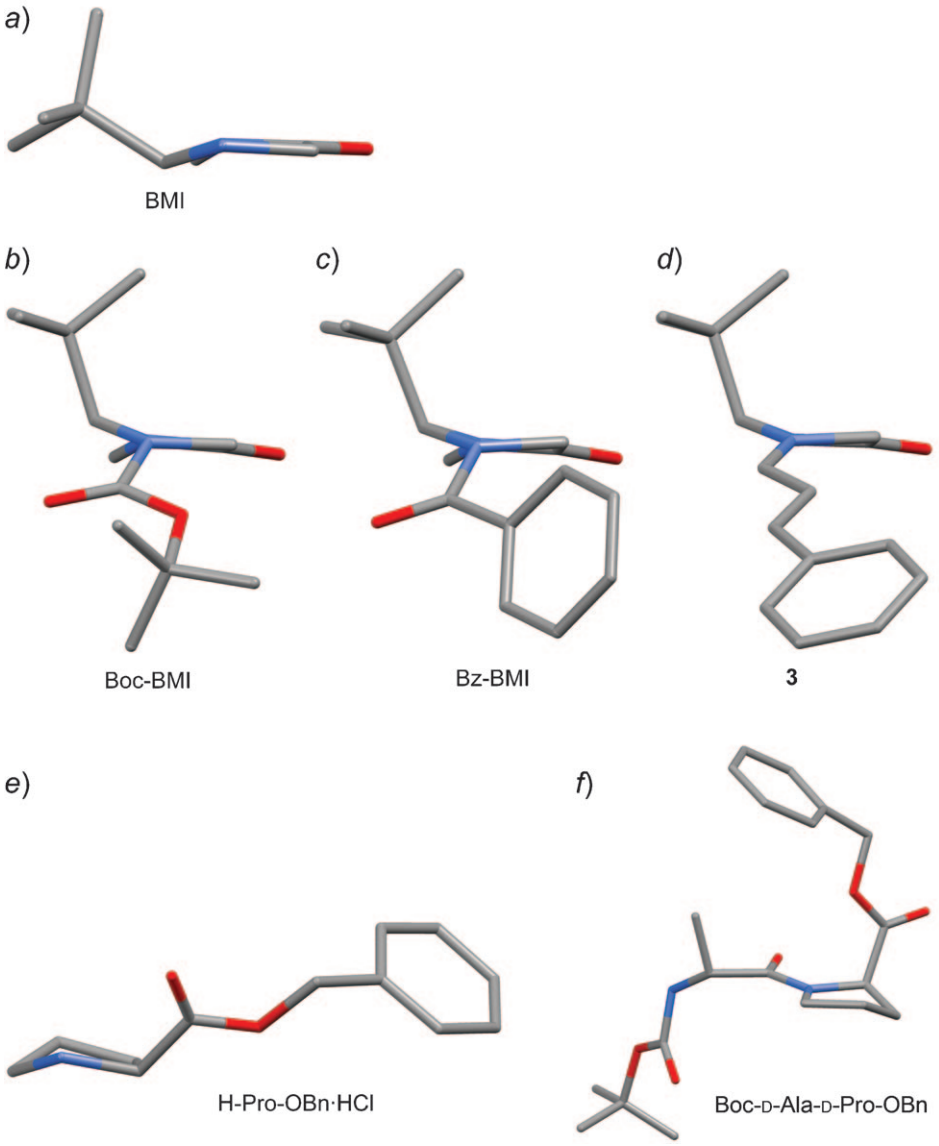

Fig. 12. *Comparison of the structures of BMI* (*a*), *with those of acylated BMIs* (*b* and *c*), *of the BMI-iminium salt* **3** (*d*), *and of proline derivatives* (*e* and *f*) *in views along the average planes of the five-membered rings.* In all cases, acylation or incorporation of N(1) into a π-system forces the neighboring substituents into a *quasi*-axial position on the five-membered ring. This establishes minimalization of 1,5-*Van-der-Waals* interaction between non-H-atoms (*cf. Fig. 9* for the analogous, more severe situation in 2,5-disubstituted heterocycles) and, in the case of the BMI-derivatives, promotes steric shielding of the π-faces by the ^{t}Bu group.

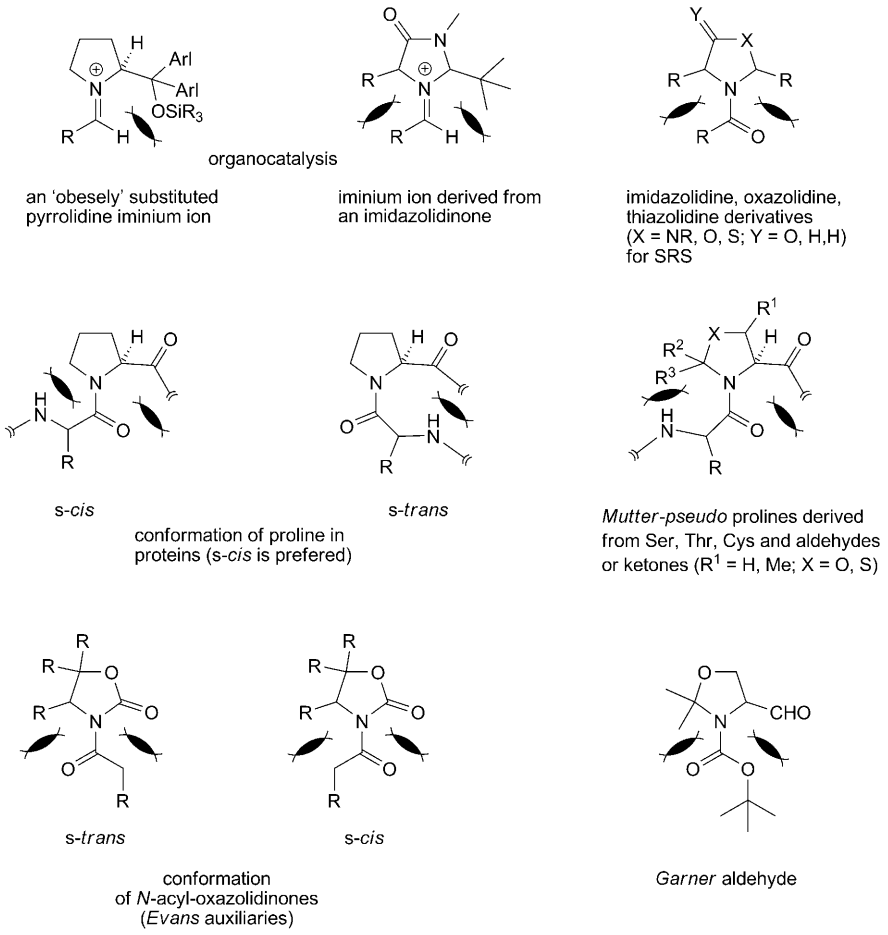

Fig. 13. *The importance of 1,5-repulsion in five-membered heterocycles with exocyclic π-systems – a structural comparison*. For leading references, see accompanying text and previous sections of this work.

instance, the use of isolated enamines or iminium salts as catalysts[39]). *The coordinates of X-ray crystal structures shown in* Figs. 1–3, 6, 10, *and* 11 *have been deposited with the* Cambridge Crystallographic Data Centre (*CCDC*)[40]).

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[39]) *Cf.* the use of an isolated, proline-derived oxazolidinone for accelerated 'proline catalysis' by *Vilarrasa* and co-workers [11b].

[40]) Copies of the data (CCDC 695934–695939) can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.]

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